

ROYAL COLLEGE OF
WITHDRAWN
LIBRARIANS OF EDINBURGH



22102165562

H.W. Dawson

Dupl

Med
K46596

THE DISORDERS OF
POST-NATAL GROWTH AND
DEVELOPMENT



Digitized by the Internet Archive
in 2016

<https://archive.org/details/b28133213>

THE DISORDERS
OF
POST-NATAL GROWTH
AND DEVELOPMENT

BY
HASTINGS GILFORD, F.R.C.S.

London
ADLARD AND SON, BARTHOLOMEW PRESS
BARTHOLOMEW CLOSE, E.C.

1911

WELLCOME INSTITUTE LIBRARY	
Coll.	weIMOmec
Call	
No.	125

PREFACE

NEARLY twenty years ago a little shrivelled boy-man was brought into my consulting-room. It was obvious at a glance that his complaint was not of any ordinary kind. He was, indeed, a most extraordinary object; but although he was afterwards often examined with the view of finding out the nature of his disease, I could not arrive at any satisfactory conclusion. Clearly the malady was not cretinism, nor rickets, nor syphilis, nor acromegaly. But what was it?

His portrait was shown to many medical friends and acquaintances, but not one had ever seen anything like him, until one day I had the good fortune to show a copy to Sir Jonathan Hutchinson. With his marvellous clinical insight he at once pointed the way to the elucidation of the mystery. Moreover, he had once seen a similar case. On referring to his description of this patient I found that while mine was of the age of sixteen years, Sir Jonathan Hutchinson's had been only two and a half years old when brought to his notice some twelve years before. It subsequently turned out that the two cases were almost identical, yet great and striking changes had taken place while the child was developing, and even now, after an intimate study of these two patients, it is a matter for wonder that Sir Jonathan should so readily have seen the connection between the child that was brought to him with cutaneous atrophy and the emaciated old man of sixteen.

I was not only furnished with the clue to the nature of the disease, but received most kind permission to seek out this old patient and make notes of his condition. Subsequently it became clear that the disease was premature old age, engrafted upon, or running side by side with, a condition of immaturity or infantilism.*

* 'Med.-Chir. Trans.,' vol. lxxx, 1897, p. 17; also the 'Practitioner,' vol. lxxiii, 1904, p. 188.

While searching about for other examples of this extraordinary malady my attention became directed to another strange condition, distinguished, not by premature old age, but by its opposite—delay of development. Though a form of infantilism, this disorder was obviously not common infantilism, for it seemed to be spontaneous in origin, and was very pronounced and uniform, deviating very little from its particular pattern. Though a species of infantilism it was quite *sui generis*; moreover, its peculiar features had not been recognised, and consequently it had received no name.* These two morbid conditions, spontaneous and premature senile decay or “progeria,” and spontaneous persistent immaturity or “ateleiosis,” furnished plenty of subject for cogitation. Mild degrees of premature old age and of delayed development are common enough, and their causes are fairly well known. But why should they occur in such an exaggerated form as to constitute disease, and why should these two diseases appear so suddenly and mysteriously and be so completely without cause, either in the individual affected or in his parents?

This opened up the larger question of the differences between growth and development, and between the growth and development which go on in the whole man, in his individual organs, and in his individual cells.

Two great inconsistencies of pathology then obtruded themselves. The first of these is to be observed in the classification of diseases. It is recognised that the microbial disorders are not peculiar to any one time of life, but may occur at any age, even before birth, though their prevalence then is limited, for obvious reasons. But when we talk of a developmental disease our thoughts immediately fly back to the period which precedes birth, as if that were the only time when development can go astray. Indeed, so closely is the word “development” associated with this period that many will regard a book written on the subject of “Development” as necessarily concerned solely with pre-natal days, and will think that the title “Disorders of Development” can only refer to club-foot, hare-lip, cleft palate, and other pre-natal morbid conditions. So that with respect both to normal and to morbid development, common opinion would lead one to suppose that at the time of birth development ceases abruptly, and that nothing more remains to be said on the subject.

That this is not a greatly exaggerated statement may be proved by asking any medical practitioner, “What are the diseases of post-

* ‘Med.-Chir. Trans.’ vol. lxxxv, 1902, p. 305; also the ‘Practitioner,’ vol. lxx, 1903, p. 797.

natal development?" and if he do not say at once "There is none," it will only be after puzzling out the subject for a time that he will hesitatingly suggest that such and such a disease is of that nature.

In this attitude he shows that he is abreast with the teaching of the highest exponents of text-book medicine, for even the best books on medicine say nothing whatever about post-natal development under the heading of "contents"; and in the text only allude to it with evident diffidence, or incidentally, as to a subject of which it is as well not to say too much.

Then there is a second anomaly of modern systematic medicine, and this also is one with which we are so familiarized by custom that it is almost unnoticed.

If we examine the chief text-books we shall find that classification in general is unsatisfactory. There is, indeed, almost as much artificiality in the classification of diseases as there was in the classification of plants before Jussieu pointed out the order into which Nature had arranged them. Though it is true that an anatomical division is used in most cases, yet evidently this is no classification of disorders at all, but of natural bodily structures. The only sections which are really satisfactory are those which deal with traumatic diseases, diseases produced by animal parasites, by vegetable micro-organisms, and by intoxications of external origin. These are satisfactory, because they go to the root of the matter, and leave us in no doubt as to the origin and nature of the maladies under consideration. But so soon as this safe ground is left behind we enter upon a veritable tangle of disorders, and are at once hopelessly lost. We meet with disease of microbial origin in juxtaposition with those due to the mechanical presence of inert foreign substances, and mingled among them a number of complaints more or less deadly in their results, due neither to toxins, nor to foreign bodies, but of whose origin and nature we know next to nothing.

The explanation is that medical knowledge has not yet arrived at a stage which admits of a completely satisfactory arrangement of disease. We can go part of the way towards it, and are then brought to a standstill before a host of complaints which cannot be made to fit into any really scientific system. On running a finger down the list of disorders drawn up by the Royal College of Physicians it will be observed that more than half lie outside the fold of a scientific classification. These outsiders are, therefore, perforce put into heterogeneous groups, each behind some organ, like a wild Highland clan behind its chieftain.

So accustomed are we to dwell upon the advances of modern

medicine that it is not easy at once to realise the full significance of the two faults or gaps to which allusion has just been made.

To emphasize the importance of the first we have only to put to ourselves the question, "Is it likely that the pre-natal period, when the immature human being is packed away within the safe shelter of the maternal womb, secure in his water-bed against mechanical injuries, more or less isolated from bacterial infections, and hedged about with effective contrivances for the maintenance of a proper temperature and nutrition, is it likely that this time of life, when so much care is lavished upon him, should be specially selected for his liability to developmental disease?"

As a matter of fact we know perfectly well that human development does not end at birth. On the contrary, it may be said only to begin at that epoch. The pre-natal period is no more than a genealogical introduction to the forthcoming chapters of development. Like the opening verses of the New Testament it has no direct bearing on the narrative, but consists solely in a condensed summary of that which has happened in earlier days. The *fœtus* is, indeed, not a human being at all, but is simply a *fœtus*. This distinction is a real one, is sharply defined at the moment of birth, and is instinctively recognised by everyone. Prior to birth the life of the *fœtus* is equivalent to that of a lower animal, and is held of very little account, especially during the earlier months. The father of a family seldom grieves when his wife miscarries, and, indeed, nowadays, as we all know, many a mother has very little compunction in taking the life of her unborn child, provided the killing can be done at a fairly early stage of its career. She is, too often, glad to escape from the incubus of child-bearing at the cost of a mere miscarriage.

But immediately after birth the *fœtus* becomes a human being, and its life is prized accordingly, so that the mother, who would without scruple ruthlessly cut short the career of her pre-natal child, tenderly cherishes that of her post-natal child. Should she deliberately destroy it, she is regarded with horror as a murderess.

In his post-natal days the offspring, having attained the status and dignity of a human being, is soon submerged in a sea of trouble and joy, discord and concord, ease and disease, each varying circumstance without exception acting upon his development, drawing him in one direction, or pushing him in another. Such being the case, is it likely that his development will escape the penalties which inevitably arise out of perversity, adversity, or ignorance?

The answer to these questions must necessarily be, that so far

from the foetus being especially susceptible to the disorders of growth and development, the probabilities are all the other way. It is in post-natal rather than in pre-natal life that most of the true disorders of development will arise.

Hence we are confronted with a large gap in pathology on the one hand, and on the other with such a superfluity of material that the classifier does not know what to do with it.

It is the object of the following pages to show that the two mutually satisfy one another—that the peg fits into the hole. It is contended that a study of the subject in its wider aspects must inevitably lead to the conclusion that most of the diseases to which we are subject are diseases of growth or of development, and that by far the larger number of them do not begin until after birth.

I have now indicated the genesis and scope of my work.

Nothing remains but to give my grateful thanks to those who have been instrumental in helping it on.

Parts of this book have appeared in various journals, and I am indebted to the Royal Medical and Chirurgical Society, the Pathological Society, the Clinical Society, the Editors of the 'Lancet,' of the 'British Medical Journal,' of the 'Practitioner,' of the 'Journal of Pathology,' and to Messrs. Wright and Sons, publishers of the 'Index of Differential Diagnosis,' for more or less altered reprints of papers, or for pictures which have already appeared in their publications.

Of these publications the 'Lancet' must particularly be mentioned, for the first sketch of my subject appeared in its pages (in 1900), and though the original articles have been much modified, they may still be said to constitute the framework of this book.

Liberal use has been made of these same journals and of others in collecting material, and I have to acknowledge above all my obligations to the 'Index Medicus' and to the valuable epitomes of the 'British Medical Journal,' of the 'British Journal of Children's Diseases,' and of the 'Medical Review,' as well as to the pages of the 'Lancet.' In nearly all cases references to other papers have been verified by appeals to the originals. Wherever this has not been done the source of the quotation is mentioned.

In the long and often tedious work of preparing these pages, mostly written in the intervals of business, I have received invaluable assistance from Miss Hart-Davis. Some of the drawings were also her work, and I am further indebted to her for the observations on old-age blood, for all my histological examinations, and for much helpful suggestion beside. Dr. Hurry and my brother, Dr. Sidney

Gilford, have given me the benefit of their skill and experience, and my thanks are also due to Prof. Keeble, who has overlooked the chapter which deals with genetics. Lastly, I am much indebted to my secretaries, Miss Uhler and Miss Langer, for their much appreciated help in the details of book-making.

CONTENTS

PART I

General Considerations

	I	PAGE
Introduction		3
	II	
Normal Development ; its Relations with Growth and Nutrition		9
	III	
Relations of Normal Development to the Cell, the Organ, and the Complex Animal		25
	IV	
The Rise and Decline of Normal Development		29
	V	
The Disorders of Growth and Development		38
	VI	
Separation of the Disorders of Growth and Development from other Diseases		46
	VII	
The Causes of Degeneration		60

	PAGE
VIII	
Distinguishing Features of the Disorders of Post-natal Growth and Development	79
IX	
Degeneration: Infantilism: Senilism: Association of Characters	85
X	
Origin of the Disorders of Post-natal Growth and Development: Variation	98
XI	
Summary ; Conclusions	132

PART II

The Disorders of Post-natal Growth and Development of Cells

I	
Introduction	142
II	
The Disorders of Post-natal Growth of Cells: Innocent Tumours	147
III	
The Disorders of Post-natal Development of Cells. Defective Development or Infantilism of Cells	152
IV	
Premature Degeneration, or Senilism of Cells—Cancers	153
V	
Clinical Characters of Cancers	160
VI	
Relations of the Cancer Process to Allied Conditions	181

CONTENTS

xiii

	VII	PAGE
Structure and Pathology of Cancer; Carcinomatosis; Multiple Cancers; Relation to Old Age		190
	VIII	
Intermediate Group		197
	IX	
Conclusions		206

PART III

The Disorders of Post-natal Growth and Development of Organs

Introduction

Section I

The Disorders of Post-natal Growth and Development of External Organs

I

The Disorders of Post-natal Growth and Development of the Extremities	218
---------------------------------------------------------------------------------	-----

II

The Disorders of Post-natal Growth and Development of the Cavity of the Nose	244
----------------------------------------------------------------------------------------	-----

III

The Disorders of Post-natal Growth and Development of Muscle	246
------------------------------------------------------------------------	-----

IV

The Disorders of Post-natal Growth and Development of the Breast	255
----------------------------------------------------------------------------	-----

Section II

The Fibrous or Prosenchymatous Group

	PAGE
I	
Introduction	261
II	
The Disorders of Post-natal Growth and Development of the Liver—Undergrowth, Overgrowth, and Defective Development, or Infantilism of the Liver	263
III	
Premature Senility or Senilism of the Liver—Cirrhosis	265
IV	
The Disorders of Post-natal Growth and Development of the Kidney—Defective Development or Infantilism of the Kidney	294
V	
Premature Senility or Senilism of the Kidney — Primary Bright's Disease	299
VI	
The Disorders of Post-natal Growth and Development of the Nervous System	314
VII	
The Disorders of Post-natal Growth and Development of the Gastro-intestinal Tract	335
VIII	
The Disorders of Post-natal Growth and Development of the Arterial System	346
IX	
The Disorders of Post-natal Growth and Development of the Uterus	354

Section III

The Cellular or Parenchymatous Group

The Disorders of Post-natal Growth and Development of Blood
and Blood-forming Organs

	PAGE
I	
Introduction	363
II	
Overgrowth of the Blood	368
III	
Overgrowth of the Thymus Gland, Spleen and Lymph Glands .	373
IV	
The Developmental Diseases of the Blood Organs—Defective Development or Infantilism	378
V	
Premature Degeneration, or Senilism of the Blood Organs .	381
VI	
Summary and Conclusions	412

Section IV

The Skeletal Group

The Disorders of Post-natal Growth and Development of the
Skeleton

I	
Introduction	416
II	
The Disorders of Growth of the Skeleton: Overgrowth .	420

	PAGE
III	
Developmental Disorders of the Skeleton: Defective Development or Infantilism	430
IV	
Premature Senile Degeneration or Senilism of the Skeleton: Osteomalacia; Osteitis Deformans; Arthritis Deformans	440
V	
Clinical Aspects of Skeletal Senilism	454
VI	
Premature Degeneration or Senilism of Joint Areas: Arthritis Deformans	462
Summary and Conclusions	466

PART IV

The Disorders of General Growth and Development

Section I

The Biological Basis

I	
Introduction	471
II	
Adaptation; Correlation; Association	474

Section II

The Post-natal Disorders of Growth

I	
Undergrowth: Dwarfism	485

	II	PAGE
Overgrowth : Gigantism		487
	III	
Correlated Overgrowth		494
	IV	
Obesity		501

Section III

The Post-natal Disorders of Sex

Over- and Under-development of Sex : Masculinism ; Feminism

	I	
Introduction		517
	II	
Overgrowth and Premature Development of Sex		521
	III	
Undergrowth and Under-development of Sex		533
	IV	
Masculinism and Feminism, or Post-natal Hermaphrodisism		534

Section IV

Centenarianism

Section V

Morbid Delay of Progressive Development or Infantilism

	I	
Introduction		545

	II	PAGE
Evolutionary or Racial Infantilism		551
	III	
Developmental Infantilism		557
	IV	
General Infantilism occurring sometimes as a Minor, and some- times as a Major Variation : Correlative Infantilism .		566
	V	
General Infantilism occurring as a Major Variation : Essential Infantilism : Ateleiosis		585
	VI	
Sexual Ateleiosis		590
	VII	
Asexual Ateleiosis		596
	VIII	
The Pathology of Ateleiosis		612
	IX	
Thyroid Infantilism : Cretinism		624

Section VI

Morbid Acceleration of Regressive Development or Senilism

	I	
Introduction		627
	II	
General Senilism occurring as a Minor Variation : Symptomatic Senilism		631

III

PAGE

General Senilism occurring sometimes as a Minor and sometimes as a Major Variation : Correlative Senilism . . .	634
-----------------------------------------------------------------------------------------------------------------	-----

IV

Thyroid Senilism : Myxœdema	643
---------------------------------------	-----

V

General Senilism as a Major Variation ; Progeria : Consecutive Senilism	645
-----------------------------------------------------------------------------------	-----

VI

General Senilism as a Major Variation—Continued ; Primary Senilism : Acromegaly	666
-------------------------------------------------------------------------------------------	-----

Summary and Conclusions

PART V

General Summary and Conclusions

LIST OF ILLUSTRATIONS

FIGS.	PAGE
1. SECTION OF GIANT HAND. BY K. L. HART-DAVIS	233
2. GIANT HAND. BY K. L. HART-DAVIS	234
3. SECTION OF PERIOSTEUM AND BONE. BY K. L. HART-DAVIS	236
4. SECTION OF LIVER. BY K. L. HART-DAVIS	285
5, 6, 7. SECTIONS OF KIDNEY. BY K. L. HART-DAVIS	311
8. EXTINGUISHED RICKETS	423
9. ACHONDROPLASIA HYPERPLASTICA	426
10. ACHONDROPLASIA HYPERPLASTICA: SKELETON	427
11. OSTEOGENESIS IMPERFECTA	434
12. SENILISM OF BONE AND MARROW	443
13. GENERAL OVERGROWTH OR GIGANTISM	492
14. PRECOCIOUS GIGANTISM	496
15, 16, 17. SEXUAL PRECOCITY	525, 526, 531
18. FEMINISM	538
19. RACIAL INFANTILISM	554
20. INTESTINAL (?) INFANTILISM	563
21. ANANGIOPLASIC INFANTILISM	570
22. A GROUP SHOWING FEATURES OF SYMPTOMATIC INFANTILISM	571
23. MICROCEPHALIC IMBECILITY: THE "AZTECS"	574
24. "GENERAL MITE," A MICROCEPHALIC DWARF	578
25. DWARFS WITH MICROCEPHALIC FEATURES: (1 AND 2) GENERAL MITE; (3) MILLIE EDWARDS; (4) PAULINE MUSTER; (5) LUCIA ZARATE; (6) THE CORSICAN FAIRY	579
26. MONGOLISM	581
27. GROUP OF ATELEIOSIC DWARFS	586
28. KEY TO FIG. 27	587
29. ATELEIOSIS, FROM LAVATER'S 'ESSAYS ON PHYSIOGNOMY'	588
30. ATELEIOSIS: "GENERAL AND MRS. TOM THUMB"	592
31. CASES OF HEREDITARY ATELEIOSIS	598
32. FÆTAL ATELEIOSIS: CAROLINE CRACHAM	599

FIGS.	PAGE
33. FETAL ATELEIOSIS: SKELETON OF CAROLINE CRACHAM	600
34, 35, 36. INFANTILE ATELEIOSIS	603, 604, 605
37. ATELEIOSIS: SKELETON OF BOBBIE FENWICK	607
38. JEFFREY HUDSON	610
39. INFANTILE ATELEIOSIS	614
40. SIDE VIEW OF THE SAME FIGURES	617
41. INFANTILE ATELEIOSIS	619
42. ATELEIOSIS OF YOUTH	620
43, 44, 45. CLAY IMAGE AND DRAWINGS OF PREHISTORIC HUMAN FIGURES	621
46. THYROID INFANTILISM	625
47. BÉBÉ, A CASE OF SENILISM	639
48. SKELETON OF BÉBÉ	641
49. PROGERIA: CASE 1, AGED $1\frac{1}{2}$ YEARS	647
50. PROGERIA: CASE 1, AGED 7 YEARS	648
51. PROGERIA: CASE 1, AGED 17 YEARS	649
52. CLAVICLE FROM SAME CASE	650
53. PROGERIA: CASE 1, AGED 15 YEARS	650
54. PROGERIA: CASE 2, AGED $15\frac{1}{2}$ YEARS. FRONT VIEW	651
55. PROGERIA: CASE 2, AGED $15\frac{1}{2}$ YEARS. SIDE VIEW	652
56. PROGERIA: CASE 2, RADIOGRAM OF HAND	653
57. PROGERIA: DR. VARIOT'S CASE	654
58. PROGERIA BEGINNING IN LATE CHILDHOOD	658
59. A CASE OF SENILISM. BY M. HARTNESS	661
60. CONSECUTIVE SENILISM	663
61. THE GIANT WINKELMEYER	672
62. BEFORE ACROMEGALY, AGED 24 YEARS	674
63. ACROMEGALY, AGED 38 YEARS	675
64. AUSTRALIAN MAN	677
65. SKULLS OF EUROPEAN, AUSTRALIAN, PALEOLITHIC MAN, AND APE	679

PART I

GENERAL CONSIDERATIONS

I

INTRODUCTION

WE must all agree that one of the most neglected departments of medicine is historical medicine. Probably the chief reason for this neglect is the existence of doubt whether anything is to be gained by it. There can be no question that ignorance of bygone medicine is not an unmixed evil; at the same time knowledge of the pitfalls into which our forefathers fell, and of the blind alleys in which they found themselves, ought to be of use, if only that we may avoid them.

The advancement of medical learning is largely dependent upon the fact that we are quite unable to take to heart the lessons taught by the experience of our predecessors. We are so satisfied with our own achievements that we are enabled to pursue our researches with the inestimable advantage of the possession of the gift of enthusiasm, such as would be lacking were we exactly to measure the extent of our progress. We of the present day undoubtedly regard ourselves with no inconsiderable degree of complacency. What doctor is there who does not look round and congratulate himself that he lives in such a time of medical enlightenment? Indeed, we sometimes wonder whether it is possible for medical knowledge to go much further. Nevertheless, it would not be difficult to find quotations from ancient medical authors to show that they had very much the same feeling. Less than forty years ago it was expressly stated by surgeons that surgical science and art had almost reached their limits. This was said just before the discoveries of Pasteur and Lister had received recognition. Since those days surgery has made such strides that it seems to many of us now that scientific surgery, instead of approaching finality, was then only beginning. Yet the lesson that we ought to have learned then, and that has been taught dozens of times before, is as if it had never been given. We are still content to peer into our present work with a sort of intellectual myopia, refusing to make use of the lens which history provides for the widening of our mental vision. If we read

medical history at all, it is regarded in its literary aspects only, and not for its educative value. Most of us only know of it as it is caricatured in the pages of 'Gil Blas,' 'Rabelais,' or 'Pickwick,' and are chiefly struck with its ridiculous theories, its nanseous medicaments, its horrible vomits and clysters, its deadly purgings and bleedings. But we fail to see that even these murderous errors of our forefathers were not solely destructive, but were in reality a necessary preparation for the work to come, and of the nature of foundation-digging. They constitute a costly experience which will never have to be repeated. We regard the work of the ancients with such a jaundiced and disparaging eye that we cannot learn from it even the elementary lesson that much as we look back upon them and their methods, so our descendants will regard us and our methods. Many of our much-vaunted synthetical medicines, our use of the meat extracts, and our indiscriminate drug-giving, will, without doubt, be regarded by those who look back from the point of vantage of a hundred years ahead in much the same way as we regard the emetics and poultices of the early nineteenth century.

Another important lesson we ought to have gathered from history has been repeated so often and with so little profit that we have ceased to notice it. This is that no good hypothesis ever becomes popular without the practice which is founded upon it being carried to excess. Of scientific import in the first place, in course of time it ceases to be scientific by becoming the basis of a dogma, opinion being held for its own sake instead of for its application. The usual career of such a dogma when it runs its full course is to conglomerate with other dogmas into a creed held by a sect, eventually to disintegrate by a species of rot, or to be displaced by another.

Only a few years ago it was the fashion to account for disease by assuming that some malign influence was at work through the agency of the nervous system. Almost every ailment not to be explained in other ways was attributed to the invidious action or inaction of impulses running along so-called "trophic nerves." Goitre, osteomalacia, chronic Bright's disease, the giant hand, cirrhosis of the liver, and many other maladies were ascribed to this cause. But we recognise now that in most, if not all, of these instances there is not a tittle of evidence for such an opinion. In most cases, indeed, it seems to have been little better than an empty assumption, having about as much basis as the popular belief in the efficacy of galvanic belts and of electricity in general. Views of this kind seem to be founded upon the fact that nerve force, like electric force, is so

mysterious and so intangible that it appeals to the imagination and affords ample scope for conjecture and hypothesis.

It has now become less fashionable to account for disease by assuming some vicious action or inaction of the nervous system. The most popular doctrine of the present day is undoubtedly the bacterial. Just as the humoral theory gave place to the nerve theory, so that, in its turn, is becoming superseded by the bacterial and toxic.

Chronic Bright's disease, acute yellow atrophy, cirrhosis of the liver, pernicious anæmia, disseminated sclerosis, progressive muscular atrophy, these and many other disorders are now attributed solely to the action of unknown toxins, and any difficulty we may have in accounting for an ailment is thought to be successfully got over by the use of that talismanic word "auto-intoxication."

But already there are signs of a coming reaction. We begin to recognise that bacteria are not of that supreme importance for harm that was at one time thought. Popular opinion still holds that the germs of disease are an unmitigated evil, serving no useful purpose whatsoever. This opinion seems to be countenanced by scientists, for apparently the chief ambition of the bacteriologist is to find some means of killing the organisms of disease without injuring the still more delicate tissues in which they grow. But it is doubtful whether this attitude is truly scientific. Disease bacteria can hardly be of such paramount and diabolical importance that they must be destroyed wherever met with, regardless of all other consequences, save the life of the animal cell. This seems to be one of the many occasions where personal dislike warps the judgment. We are apt to think that whatever is hurtful or offensive necessarily contains a preponderance of evil. But a little consideration must soon reveal the falsity of this position. The result of the complete destruction of disease-producing organisms becomes evident if we consider the economics of such a process as that of putrefaction. Decomposition is usually offensive. The very word is suggestive of filth, garbage, and stinks. Nevertheless, we all recognise that the bacteria which give rise to these unpleasing results fulfil a highly important function. They break up and dissipate waste organic material, and so do service to the living organisms remaining. Exactly the same principle obtains in regard to disease. The healthy, vigorous human animal dwelling in clean surroundings lives happily to a good old age, no microphytes of disease being able to gain a footing in his body. But let him lower the vitality of his tissues by excesses, by sloth, by overcrowding, or by habitual uncleanness, and he becomes

in a minor degree like the refuse. In such a case "'tis better not to live than wretchedly not thrive." He is not calculated to maintain and continue life at the standard which is to be desired. Hence, like the dead refuse, his only partially vitalised tissues become the prey of bacteria. The decomposition of disease sets in, and encroaches upon the living tissues until life itself is driven out, and the whole body is handed over to the bacteria, which reduce it to its primal elements. Dissolution, in fact, is a process which begins, not at death, but as soon as lethal bacteria gain a footing in the living body. That bacterial disease within the body is due to the same process as putrefaction outside the body is proved, if proof be needed, by the fact that occasionally the same species of organisms officiate in both capacities. Indeed the parasitic bacteria of disease are probably all saprophytic, and when cultivated outside the body tend to become harmless. But having in this way changed into saprophytes they may again be turned into disease parasites by means of repeated passages through the body.*

Looked at in this way we see that as "prevention is better than cure," so the higher aim of the surgeon is to be aseptic rather than antiseptic, and of the physician to foster the health of the cell, rather than to attend primarily to the microphytes which attack it. Such a view exhibits the bacteria in a very subordinate position, and the cells of the human being in a correspondingly high place.

While we may come to the conclusion that in the study of medicine the bacteria are of less importance than the cells and tissues they infest, it is equally necessary to realise that these tissues and cells are far more independent than was at one time thought. The tendency of recent knowledge is to point more and more definitely to the first importance of the cell, and of cell communities, or organs, in the politics of the body. The human political system is essentially liberal and progressive in recognising to the full the importance of home rule or local government in all local affairs. One outcome of this local self-government is that disorders may occur in the provinces of the body without having any material effect on the body at large. Thus, in muscular dystrophy, whole groups of muscle may be thrown into a state of insubordination without seriously affecting the general health, and the same may be said of tracts of skin in ichthyosis, of bone in osteitis deformans, and of nerve tissue in locomotor ataxia. It is not until disorganisation is sufficiently extensive, or encroaches on parts of vital importance, that the seat of government is affected by the damage which is being done in the confines

* Prof. Klein, 'Brit. Med. Journ.,' 1904, vol. ii, p. 1509.

of its territory. The part played by the vascular or nervous system in these disorders is of secondary importance; they are primitive affections of the organs themselves. It is with the diseases of this nature that we are now about to deal. An attempt will be made to show that they have certain important characters in common, are formed on the same plan, and belong to the same group, though each member retains its own individuality.

Prior to the nineteenth century the usual conception of disease was to the last degree hazy. All that could clearly be seen was fog. Disease was disorder itself, and out of this general confusion it was possible to separate many disorders much in the same way as by close observation the fog of one hollow could be distinguished from the fog of another hollow. But in course of time it became obvious that that which appeared to be the very negation of method was in reality the outcome of perfect and sustained order.

For example, malaria was attributed to an unknown miasm rising in an unknown way from some conjectural poison lingering in the soil, or rising as an effluvium into the air of marshes. The theory of marsh fevers was, in short, as misty as the marsh air, which was assumed to be their carrier. Nowadays we know that malaria is the manifestation of a normal life cycle of an animal, and its biological changes are pictured in our text-books with about as much detail and precision as if they were designs for a wall-paper.

It is after this fashion that all progress has been made in medical science. The material of disease is at first, like the nebular world, without form and void. It seems to be an aimless, gratuitous infliction of evil, so that we still hear from those whose leanings are literary rather than scientific of the "mystery" of pain and suffering. We observe that the order which ultimately arises out of this chaos is invariably of one sort: everything is reduced to terms of biology. In the place of the old-time mind-fog associated with the words "malaria," "tuberculosis," "scabies," "typhoid," we have the clear biological conceptions which gather about the life-histories of the animals and plants which produce them.

Whatever may be said in this respect of the flora and fauna of the body is equally true of the body itself. All the real epoch-making advances were biological. Schwann discovered the human cell; Virchow showed the modification which the cell undergoes in pathology; Hunter attacked the problems of disease from the biological side, and the recent discoveries in cytology and immunity

by Professors Ehrlich and Metchnikoff, and by Sir A. E. Wright, are biological.

Evidently, therefore, in dealing with the subject of the diseases of post-natal growth and development it must be our object to harmonise all the facts with the common laws of life. We must begin with the assumption that they not only have their foundation in biological events, but are themselves of the same order. As our leaders we must look not only to the clinicians and to the laboratory pathologists, but to such men as Darwin, Galton, Mendel, Bateson, and must regard them as as truly pioneers of medical science as Sydenham, Tronseau or Laennec.

We see, in short, that the diseases of growth and of development can hardly stand apart from the ordinary processes of life, but must themselves be biological, and as useful and necessary in their way as other biological phenomena.

Biology, then, must, after the manner of "Knowledge," in 'Everyman,' be our guide, as we thread our way through the intricacies of the diseases with which we are now concerned.

The method adopted is to devote the first part to an explanation of the terms "growth" and "development," and to a definition of their diseases. In so doing it will be seen that these disorders are essentially natural processes dislocated from their proper setting, and either falling short of their proper degree, or carried to an unhealthy excess.

The rest of the book consists in the application of the axioms, rules, or generalisations gained, first to the disorders of growth and development of cells in their individual capacity (Part II), then to organs (Part III), and lastly to the whole complex organism (Part IV).

The object has been not merely to accumulate facts but to marshal them into an orderly sequence, causing them, as befits a work on growth and development, not only to grow by a process of organised accretion, but also to develop, the one part depending upon the part which goes before, and paving the way for the part which comes after.

Here, therefore, is the place in which to request that anyone who reads this book will refrain from drawing conclusions derived from pieces taken at random, or selected from the middle or end, but will have regard to the natural sequence of the argument.

II

NORMAL DEVELOPMENT: ITS RELATIONS WITH GROWTH AND NUTRITION

Immunity is the best criterion of *nutrition*. *Growth* is a quantitative process; *development* qualitative. There are two kinds of development—ontogenetic and phylogenetic. Development is co-terminous with life, and is either progressive or regressive. Regression implies a repetition of progressive phases in reverse order. The structural changes of senility consist in the return of cells and tissues to their primitive simplicity.

IN studying the diseases of the involution and of the decline of life, it is of the highest importance that we should first understand the nature of these processes under normal conditions. Evidently the property or attribute of organic life which we term *development* does not stand alone. In the healthy organism it is closely bound up with *growth* and *nutrition*. These three are often confused in the mind, but we cannot too clearly understand that they are in reality distinct processes. Growth, nutrition, and development form a trinity. Like the three primary colours of the spectrum each has an individual existence, but under natural circumstances is so blended with the other two as to lose its identity. The relation between them, though intimate, is variable, so that sometimes one predominates and sometimes another. Thus we may have excess of growth or defect of growth, while nutrition and development remain almost unaffected. Growth may be excessive, nutrition poor, and development of low type, or *vice versâ*, and similarly with nutrition and development. In health this variation is always kept under control, so that no one of the three obtrudes itself. The relation between them varies with the age of the organism and its position in the animal kingdom.

Before going on to speak of our principal subject—development—it will be necessary to refer a little more particularly to growth and nutrition.

Growth.

Organic growth is of two kinds. There is, first, individual or somatic growth—the accumulation of cells by and within the individual; and secondly, there is reproductive growth, brought about by the separation of particles to form offspring. As a rule the lower the development of the plant or animal the more nearly do those two forms of growth approach each other, until in some unicellular organisms (*e. g.* yeasts, amœbæ) they seem completely to merge one into the other.

Reproductive growth becomes less and less vigorous as we ascend the scale of organic life. The herring has millions of offspring, man but one or two. On the other hand, individual growth tends on the whole to become greater as development ascends. Hence the relative sizes of man and herring. But the inverse relation between the two forms of growth is unequal, for speaking broadly, the sum total of growth becomes less as the scale of development rises.

The influence of age upon growth is in great part bound up with the decline of development and of nutrition. In old age the union between the trio (growth, development, and nutrition) is not so close as it is at other periods of life. They tend to part company. Growth itself becomes unbalanced or irregular as age advances; the rise of growth in early life and the equilibrium of maturity are followed by the leanness or fatness of middle age, and this inequality becomes still more accentuated in old age.

Nutrition.

The word “nutrition” is not now used in its special relation to food or feeding, but to a condition which is in part the result of the assimilation of food and in part of factors of whose nature we know nothing. “Vitality” is perhaps a better word. Nutrition or vitality so understood expresses itself in growth, in development, in pigmentary, fatty or other molecular changes, in responses to electric and other stimuli, in movement, and above all, in phagocytic or opsonic power. But the term “nutrition,” even when used in this more restricted sense, is unsatisfactory, for it is evidently being applied to processes which may differ widely in their nature. Nevertheless, as this is not a work on nutrition, we shall continue to use the word in the same indefinite way as that to which we have been accustomed.

A good criterion, then, of the state of nutrition of any organ or

part is the extent to which it resists bacterial poisons. It seems pretty evident that the resisting power of both vegetable and animal organisms bears no definite relation to their normal growth or development. The relation is more or less capricious. One animal or plant may be hardy and show great power of resistance to the attacks of micro-organisms; another, of a closely allied species, may, under similar circumstances, be very delicate, and readily succumb.

Among the lower forms of animal life the destruction by higher animals is so great that it is impossible to say what their tissue vulnerability to bacteria is under normal conditions.

Animals artificially protected from the larger and fiercer beasts which naturally prey upon them seem to be very prone to succumb to bacterial disease. It has also been pointed out by Bates, Stanley, and other travellers that highly civilised white men withstand disease and the hardships of tropical travel better than savages. This is the more remarkable, as it is to be supposed that in many cases long custom must have established some sort of immunity among the natives. But in these cases there are so many circumstances to be taken into consideration that they lose much of their value as evidence of comparative immunity.

Development.

Comparison between Growth and Development.

No headway can be made with our subject until we have a clear conception of what constitutes growth and what development. These two are so often confused that we need no other excuse for dwelling upon their differences in a way which may seem elementary, not to say tedious. Growth is mere augmentation or increase. It is a quantitative change only, and has nothing to do with quality. Development, on the other hand, is evolution or unfolding, and is a qualitative change pure and simple, with no relation to quantity. If we have a heap of clay sufficient to make a house and then form it into bricks and tiles, and with these bricks and tiles build the roof, walls, chimneys and other parts, we have a good illustration of the difference between growth and development. For in the process of building, the heap of clay, though it has expanded, has not grown in the slightest, but yet has undergone very conspicuous development. Hence in the ordinary work of building a house there are two distinct processes going on together—one is the process of growth by the piling of brick upon brick, and the other running *pari passu* with it is that of

continuous or progressive development. Out of the same quantity of clay a house may be built, either of sun-dried bricks of the crudest possible form, or of well-baked bricks arranged into a house of the most perfect architectural design. Both may be said to be alike in their growth, though there is a vast difference between the development which ends in the adobe hut and that which ends in the "bijon family residence" or the "country seat" of the estate agent.

So also a normal man of 1·8 m. in height is not in reality better developed than a normal man of 1·5 m., though it is commonly said that he is. His growth is bigger but not his development. Size, it is true (as well as shape and proportion), is one of the indications of development, so that we may be right in saying that a well *grown* man is of better development than the little man who is in other respects his equal. But, place the little man of good proportions, who may be a Gladstone or a Wellington, side by side with a big Soudanese or even with the average European, and we have no hesitation in saying that the little man is in every respect—mentally, morally and physically—the better developed of the two. The development of the Caucasian is higher than that of the negro race, though possibly the latter may be bigger. So also is the man in every way better developed than the elephant, though the latter has more substance, more muscle and bone. Size, in short, is no criterion of development except in a minor degree. Development is in the main qualitative, and growth quantitative.

Two Kinds of Development—Ontogenetic and Phylogenetic.

The development of an animal is divided into two kinds, to wit, ontogenetic or individual development, which deals with the evolution of the animal from the germ-cell to the perfect form; and phylogenetic development, which is concerned with its genealogy from the dawn of life to the formation of the most advanced species.

Ontogenetic development.—It must not be forgotten that there is no real difference between evolution and progressive development. Hence, all the different phases which are passed through during the evolution of any particular species are recapitulated in the development of every individual of the same species. This is admitted to be the case in the pre-natal period, as was shown by von Baer. The successive phases in the development of a foetus of any animal are the representation in miniature of the stages of its evolution. But it is equally true of post-natal development, though its phases are not so conspicuous. Roughly

speaking, we may say that pre-natal development carries the human being up to the stage corresponding with that of the dividing ground between the higher apes (or by whatever term we signify the immediate progenitors of our species) and the lowest races of mankind. The birth of the child corresponds with the birth of humanity, and the progressive steps of post-natal development continue the evolution of the individual through stages which correspond with arboreal, savage and semi-civilised life, up to the highest civilisation to which the accidents of race, nation, heredity, education, and the personality of the individual are capable of raising him. Hence there are important practical differences between the pre-natal and post-natal eras of development, for whereas the pre-natal periods may be regarded as for all practical purposes almost outside the limits of direct human effort, this is not the case with post-natal development, because the post-natal animal is in the malleable stage, and is capable of being shaped into an instrument of any degree of utility.

Development and degeneration are often spoken of as if they were two distinct processes. This is not true; they are merely different phases of the same process. There is no line or even area of demarcation between them; they run one into the other. Professor Huxley's words on this subject are very much to the point when he says "development and life are, strictly speaking, one thing; though we are accustomed to limit the former to the progressive half of life, and to speak of the retrogressive half as decay."

Instead, therefore, of regarding development and degeneration or youth and old age as two different physiological processes, it would be much more accurate if we regarded the whole procession of life as one of development, the first part of progression, and the last of retrogression. This will seem the more fitting when we remember that after middle age some of the main features of development recur in the opposite order. After maturity, as vitality declines, we can often trace a second youth, and, following upon that, a second childhood and a second infancy. A second puberty initiates the second youth, and is more abrupt and pronounced and earlier in women than in men. Just as the first puberty is a time of mental and physical stress, and is marked by an outgrowth of bodily and facial hair, and the first appearance of the sexual functions, so the onset of the second youth is distinguished by disturbance of the reproductive system, both primary and secondary, and by renewed outgrowth of hair on different parts of the body. In some branches of the yellow race, beard and moustache are hardly visible until this

time, so that in their case the so-called sexual hair scarcely appears until the sexual organs have decayed. In white women there is often a similar, and very unwelcome, outgrowth of facial hair at the time of the second puberty. Further, in both sexes there is sometimes a distinct increase of sexual desire just before the extinction of the reproductive functions, like the flare-up of a candle before it goes out.

At the onset of second childhood the male sexual organs decline, so that the man gradually returns to the neutrality of pre-pubic days. The whole muscular system weakens, though the weakness usually shows itself chiefly in the lower limbs, and the old man once again in his life walks with difficulty. The perambulator stage of existence returns, though the perambulator is now called a bath-chair. The mind becomes childish, and the forgotten events of long passed days come back to the memory, so that the old man lives his youth and childhood over again. The hair falls off, mastication is accomplished by the gums, and there is a return to the soft foods of early life. The voice becomes piping, querulous, or shaky.* The sphincters weaken, so that control of the evacuations is imperfect. Sometimes the old man or old woman reverts to a state of infancy and to babyish diet, and, being unable to talk, cries and whimpers for whatever is wanted.

A good, but unsympathetic picture of the neglected old man is given by an ancient writer, Richard Rolle de Hampole, in his 'Pricke of Conscience,' written about the year 1340.

<i>Fone</i> men may now fourty yhere† pas,	[<i>few</i>
And foner fifty, als in somtym was;	
Bot als <i>tyte</i> als a man waxes alde,	[<i>soon</i>
Than waxes his <i>kynde</i> wayke and calde,	[<i>nature</i>
Than chaunges his complexcion	
And his maners and his condicion;	

* "The gradual degeneration of speech may be traced in the case of old men who gradually pass down the incline into senility. Study of the speech of such persons shows that the degeneration of their faculty retraces the steps by which it has been progressively acquired." "Sur l'Evolution regressive de l'entente chez certains aliénés," 'Bull. de la Société d'anthropologie de Bruxelles,' v, 1885, 1886. Quoted by Demon, Massart and Vandervelde, 'Evolution by Atrophy,' p. 177, Mr. Mitchell's Trans.

† Montaigne, writing in the sixteenth century, says: "What said Cato Junior to those who sought to hinder him from killing himself? 'Doe I now live the age wherein I may justly be reproved to leave my life too soone?' Yet was he but eight and forty yeares olde. He thought that age very ripe, yea and well advanced, considering how few men come into it."—*Florio's translation*.

Than waxes his hert hard and hevy,	
And his <i>heved</i> feble and dysy ;	[<i>head</i>
Than waxes his <i>gast</i> seke and sare ;	[<i>spirit</i>
And his face rouncles, ay mare and mare ;	
His mynde es short when he oght thynkes,	
His nese ofte droppes, his hand styntes,	
His sight waxes dym that he has,	
His <i>bax</i> waxes croked ; stoupand he gas	[<i>back</i>
Fyngers and taes, fote and hande,	
Alle his touches er tremblande.	
His werkes <i>for-worthes</i> that he bygymes ;	[<i>are worthless</i>
His hare <i>moutes</i> , his <i>eghen</i> rymes ;	[<i>moults ; eyes</i>
His eres waxes deaf, and hard to here,	
His tung fayles, his speche is nocht clere ;	
His mouth slavers, his tethe rotes,	
His wittes fayles, and he oft dotes ;	
He praises ald men and haldes tham wyse,	
And ylung men list him oft despyse ;	
He loves men that in ald tyme has bene,	
He <i>lakes</i> tha men that now are sene ;	[<i>blames</i>
He is ofte seke and ay <i>granand</i> ,	[<i>groaning</i>
And ofte angerd, and ay <i>pleynand</i> .	[<i>complaining.</i>

Old men, like children, often show great lack of self-control, and are guided to a large extent by their emotions. Anger, irritability, and grief are no longer under their former restraint, and the old man easily becomes emotional, talkative, or even garrulous. Some old people are more or less inebriated with their age. They lose all care and depression of spirits, and become sunny in disposition, so that they readily laugh and smile. All harshness of judgment disappears, and the happy benignant mellowness of the old man who is at peace with himself and with the world constitutes one of the chief attractions of second childhood. We feel as easy and as restful in the society of such old men as we do in the company of children, and perhaps nothing is more charming in both the very old and the very young than the complete absence of that distrust and harsh criticism which so often act as a barrier between one human being and another.

Sometimes senile decay is associated with but few of the signs of childhood ; at others they form its most noticeable features.

We have in our mind a charming old man of eight-four, who shows this reversion to youth and childhood in a marked degree, at times greatly to the concern of his family. His memory carries him back to his early days that

he seems to live in the past rather than in the present. So real to him is this mental picture of his boyhood that he often talks of his boyish companions as if they were still living, and has even gone so far as to put aside a pocket-knife for some old-time playmate, who died when they were youths together. At one time his return to youth took the atavistic form of tree-climbing, leading, on one occasion, to an ugly fall. At other time he takes the long aimless walks indulged in by boys, missing meals and getting back dog-tired at the end of the day. Some such escapades as these have led to his being treated with restraint. But this is not very successful, for, although he will sit by the hour doing nothing, and apparently thinking of nothing, such bouts of good behaviour are regarded as of bad omen, for it has been noticed that if he has afterwards been left alone for a few minutes he will "bunk" off into the woods. On one such occasion he was seen furtively running in a doubled-up position under the shelter of a hedge, until he had got behind a wood-pile, where he remained hidden until the danger of pursnit had passed by. His return after such an act of insubordination is very shamefaced. He creeps in by the back way, and makes sorry attempts to appear unconscious of wrong-doing. Once, when spoken to about his misdeeds, and accused of behaving like a wilful and disobedient child, who does wrong and is ashamed, he clapped his hands on his knee, exclaiming: "That is exactly what I think about it. I feel just as I used to feel after I had played truant from school."

Some of the features of the old man's return to childhood tend to show that this period may be quite as reminiscent of a prehistoric existence as are many of the incidents of the first childhood; they serve to prove the reality not only of a descending development, but also that the descent tends to bring the human being back to a time of life which is filled with memories of instincts acquired during the early ages in the evolution of his species. In other words, it is a true retrogression. Of course such an extreme degree of second childishness as that just mentioned is closely allied to disease, and will no doubt pass on into senile dementia.

The nature of senile degeneration is well shown in its effects on muscular co-ordination. The young baby is as erratic in his movements as a butterfly, but gradually as he passes through the stages of life and experience is acquired his movements become more sure, and, if the training continue, by the time he has reached the climax of development he may have acquired a control of muscle so accurate as to rival the unflinching precision of machinery. But as age creeps upon him this nicety of co-ordination fails, years of accumulated experience are stripped off; and gradually, step by step, he goes back once more to his old inco-ordination. His hands shake, his head nods, his voice quavers, and all his movements become uncertain, the

more highly developed or last acquired faculties leaving him first, until the old man is left with about as much co-ordination as when he started.

This incoordination is not physical alone, but is mental as well. The painter or draughtsman, who combines hand-work with head-work, when his faculties decline in old age, loses originality, becomes crude in design, and inaccurate and slipshod in execution.

Once senility has set in the judgment of the man of business cannot be depended upon. Many a large fortune accumulated by the shrewd, calculating patience and enterprise of middle age has been squandered by the miscalculations and extravagances of old age. The recklessness of the one extreme of life differs only in detail from the recklessness of the other extreme. The bad judgment of youth is the result of defective development and lack of experience; that of old age is the result of the arrival at a corresponding stage of failing development, when experience is forgotten.

Structural Changes in Senile Decay.

It is impossible that such profound changes as those which denote the declining stages of development can be changes of function only. They must of necessity have their origin in some corresponding alterations of form. The outward manifestations of second childhood are, in truth, the result rather than the cause of structural changes—changes which also remind us of the structural peculiarities of early life. In the great internal organs the more highly specialised secretory cells tend to become fatty and to lose their function, while the lower order of cells and tissues—the connective tissues—tend to increase, and so once more to bring the glands back to a period of their early development, when specialisation was beginning, and a low type of cells predominated. The kidneys and liver of the old are not only wasted, but a definite alteration has taken place in their cells in regard both to quantity and quality. The secretory cell is smaller and simpler, and numbers of interstitial cells of embryonic type have made their appearance. Most of these latter form themselves into new connective tissue. As it is with the liver and kidneys, so is it with other organs of their kind. Special organs show special features, but one and all express their degeneration by a simplification of structures of higher type on the one hand, and by the appearance of a more primitive type of cells or tissues on the other. It is particularly to be noticed that the specialised cells, such as gland-cells or nerve-cells, do not break down without method, but decay

first at a distance from their nuclei, the nuclei being most resistant of all. This is best shown in the cells of highest development, as has been pointed out by Dr. Webb in the case of the giant-cells of Betz. These break down at their periphery first, the protoplasm round the nucleus remaining unaffected until quite late in the progress of decay. Generally speaking, it is the periphery which gives the character to the cell, and the nearer one gets to the nucleus the less specialised is the cytoplasm which surrounds it. All cells, however high their position in the scale of complexity of function, start as simple, rounded bodies without processes; but as evolution goes on they tend to add to their cytoplasm, to become bigger and more angular, like liver- or kidney-cells, or to branch out into processes, like bone-cells, or like the ciliated cells of mucous membranes, or like brain-cells. In fact, cell civilisation in the concrete, as well as in the abstract, is an accretion, for that which is last acquired tends to take up a position on the outside of the cell. The natural result is that, when senile dissolution sets in, the cytoplasm close to the nucleus is the most stable of all, and is the last to break down, whereas that which is situated away from the nucleus tends to degenerate sooner. From this it will be obvious that when a cell of high type undergoes the disintegrating changes of old age it reverses the order of its development. The peripheral parts which represent the more advanced acquisitions of maturity go first, and then those which correspond with the state of the cell in youth, the cell being then gradually reduced to the simplicity of its embryonic state, before it started on its special career. It does not necessarily follow that this process of simplification can always be detected in the size and shape of the cell. The senile cell may be quite as big or even bigger than it was in the prime of life. Nevertheless, it is, to all intents and purposes, smaller and rounder, for the granular and fatty changes which have distended its protoplasm are peripheral rather than central, and the only useful part is that gathered about the nucleus. But it is not in accordance with the sanitary economy of the body that effete material should be permitted to remain long untouched. Some process of denudation, therefore, goes on at the circumference, so that, as a rule, the size and shape of the cell are ultimately made to correspond with the particular stage of retrogression at which it has arrived.

That this downward or backward march of the cell is a reality is proved by the way in which its activity is retained throughout the whole process of reduction. Thus, in a liver which is becoming senile, all stages of simplification of secreting cells can be made out, from the large, polyhedral, fully developed cell to the small, round

cell, consisting almost solely of nucleus. These reduced or simplified cells do not remain idle, but show their vitality by proliferating: and they not only perform this primitive function, but, according to Professor Hamilton, proceed to another duty which devolves upon cells of simple construction. They apparently become the constituents of fibrous tissue. So also in bone, which is wasting as the result of old age, a similar retrogression and similar activity of cells can be followed out. The bone corpuscle, with its many branches which began life as a simple, rounded osteoblast, under the influence of old age loses its processes and sinks again to its osteoblastic stage. Only now, in accordance with the natural fitness of things, its function is reversed. It is no longer a bone-former or osteoblast, but a bone-destroyer or osteoclast. Even in the intermediate stages of simplification the cell is still functional. This is well shown in the case of the liver-cell, which in the course of degeneration may sometimes be seen assuming the square shape of the tube-lining cell, and may even combine with others to arrange themselves into the semblance of a duct. Though this appearance is best seen in cirrhosis, particularly in hypertrophic cirrhosis, yet it is also to be made out in the senile liver. It seems to indicate that in the course of its retrogression the liver-cell arrives at a stage at which it is incapable of doing the work of a gland-cell, and is yet too highly developed to undergo transformation into connective tissue; it therefore assumes the shape and offices of the inferior epithelium peculiar to ducts. The real significance of this change will be gone into when we deal with the diseases of the liver.

Such facts as these tend to show that in the course of senile degeneration the changes in the form of the cell exactly tally with the changes which take place in its function. The parts which indicate complexity and specialisation give way first, and in the order of their building up, finally leaving only those elements which go to the making of a simple cell—that is, the nucleus, with a small quantity of protoplasm around it. In other words, degeneration and retrogression of development are one and the same process, both in the structure of the cell and in its function.

We are now provided with two generalisations of great importance. One is that *senile degeneration and retrogressive development are identical*; and the second is its corollary, for it follows in natural sequence—the tissue changes of old age are known quite as much by the re-appearance of embryonic characters as by actual decay. In this proposition and its corollary we have the keystone of the whole subject of the perversions of development.

It may be said of some forms of life that they never die a natural death. Some unicellular animals and plants divide indefinitely and so live for ever. So also is it true of an oak tree or of any other exogen, that no provision has been made for its spontaneous or automatic extinction. So long as it escapes the attention of the woodcutter, or the ravages of fire or storm, or resists the encroachments of other forms of life, it goes on living and growing for ever.

But the same cannot be said of the higher animals. Provision is made for their automatic and painless extinction, as soon as their period of usefulness is over. This euthanasia, as we have just seen, is brought about by a reversion of development, so that second infancy is naturally followed by second birth. The actual mechanism of this painless death varies, but is probably nearly always ultimately an affair of the heart or the brain. Often the climax appears to arise from interference with the nerve centres which control circulation and respiration. Their ganglionic cells are apparently worn down and simplified until function at last comes to a standstill. In rare cases this is all, but as a rule the process is helped by some lingering catarrh, some pneumonic change in the lungs, a little indigestion, or slight nervous disturbance. At other times the poor mortal undergoes a process of beneficent pole-axing. The same retrogressive changes which cause fibrosis of his muscles, and of his liver, are at work in his arteries. The resilient, elastic tube, yielding or contracting in sympathy with every requirement in its particular area, becomes simplified but deformed into a coarse, rigid, brittle pipe. A leak ensues, and provision is made that this leak shall take place just where it is least painful and most effective, that is, in the great central nerve connections of the brain.

There is much difference of opinion as to the uses of the embryonic cells which appear in senile organs. Metchnikoff* suggests that they are phagocytes, and that having overcome all the microphytic invaders, they next attack and devour the higher elements of the body, and so produce senile decay. He pictures a section of a renal tubule invaded by "macrophags," and also a "cell from the brain of a woman 100 years old being devoured by macrophags." This view is, of course, not generally accepted. Even if the higher cells are removed by a process of phagocytosis, which is disputed, it does not follow that "senile decay is mainly

* 'The Nature of Man,' Trans. Dr. Mitchell, p. 241.

due to destruction of the higher elements of the organism by macrophags," as Metchnikoff asserts. That molecular decay of these cells occurs first, and that the phagocytes merely remove the effete material, seems far more likely.

In a gland undergoing senile decay and containing cells not required during its youth and maturity, it is by no means easy to say whether these cells are invaders or are derived from the organ itself, and have undergone the process of simplification. Some of them are apparently derived from the proliferation of connective-tissue cells or of endothelial cells, and others from the multiplication of gland-cells, which have been reduced almost to a bare nucleus. But mingled with them are large clear cells, each containing a single nucleus. These are mononuclear cells derived from the blood, and are also denominated macrophags by Metchnikoff. But according to Dr. Muir* most of the invading cells from the blood belong to the small variety of lymphocytes. They are a lower type of cells, and contain such a small quantity of cytoplasm round their nuclei that though to some extent possessed of phagocytic power, they are to all intents and purposes non-phagocytic.

It is by no means easy to observe the act of phagocytosis, for one may examine many sections from a senile organ before it is possible to see a mononuclear or fibroblast so placed, in regard to a secretory cell, that it can be identified as a phagocyte in process of absorbing the outer substance of the cell. But it cannot be doubted that the cells, as we see them in the artificially prepared slice under the microscope, are not as they exist in nature; they are, perhaps, no more like the living cells than are the dried plants of the *hortus siccus* like the living plants. It is, therefore, not to be inferred that because cells are not to be caught *in flagrante delicto* the act of cannibalism is not to be proved against them. When the palæontologist picks up out of the drift-gravel a much chipped stone, rudely fashioned into the shape of a spear-head or "celt," and asserts that it was made by man, we are convinced of the truth of his statement because we know that no possible combination of fortuitous friction by other flints could have brought about such a result. So, also, when in a section of a senile liver we see numbers of sharply defined cells in all stages of reduction, from the perfect polyhedral cell to the almost naked nucleus, we must admit that this alone is good circumstantial evidence of phagocytosis, for we do not know of any other process in the body which could so act on a cell as to produce such a result. And this must hold good even if

* 'Brit. Med. Journ.,' 1904, vol ii, p. 585.

the cell in the intermediate stages is, as a rule, rounded off and smooth, and is only rarely mouse-eaten or chipped, such as we expect it to be. Then, again, there are large mononuclear cells which have strayed from the capillaries, and whose mere presence is an indication that they have been engaged in this work of absorption. It is as if we not only see the flints bearing the marks of design upon them, but also in their neighbourhood the skin-clad savage himself, not engaged in making or using them, it is true, but living a life which is entirely dependent upon the use of just such implements as these.

In a later work Metchnikoff* draws attention to the criticisms of M. Marinesco, Lire, Voisin and others who have failed to find evidence of phagocytosis of senile cells. But Metchnikoff declares that their failure is due to faulty methods, whereby the cytoplasm surrounding the nuclei of the phagocytes has been destroyed. He asserts that M. Manonelian, by means of an improved technique, demonstrates the macrophags *in situ* and in the act of phagocytosis, and illustrates his paper with drawings of phagocytes engaged in this process of peripheral absorption.

Just as civilisation is, according to Carlyle, largely a matter of clothing, or, at any rate, of accretion, so the accumulations of knowledge and experience which were last acquired are the first to go as the character degenerates. So also is it with the cell, and the phagocytosis is merely a sanitary procedure, having for its sole object the removal of deteriorated, waste cytoplasm.

In the senile organ we see, in principle, exactly the same process going on as there is in the removal of an aseptic slough. It is true that in the one case the material to be removed is dead and is in one uniform mass, while in the other it is only old, decayed, or half dead, and still forms an integral part of normal living tissue distributed in an orderly manner, such as befits the tissues of an organ. But in both cases phagocytes are at work, and side by side with the phagocytosis we see also the building up of new tissue replacing that which is destroyed. In the case of the slough this is carried out by just such plain cells as are present in the senile organ. These migrate into the part or are proliferated out of the neighbouring connective and endothelial cells, and ultimately reconstruct the lost part, not, it is true, after the original pattern, but after a far lower type of tissue, which we recognise as scar-tissue. So also in the liver or kidney undergoing senile degeneration; the ultimate result is of the nature of a scar. The peripheral decay of secretory

* 'Prolongation of Life,' Trans. Dr. Mitchell, 1907.

cells, which is apparently the initial cause of the change, is spread through the whole of the organ or organs and is not focussed on to one point. Moreover it comes at a time of life when vitality is at its ebb, and so it generally happens that the retrogression of so many of the special cells of an important organ does not go on long ere function is so seriously interfered with as to put a stop to life itself, before there has been time for any large amount of fibrosis. Perhaps all that is noticed in such aged tissues is that the muscle, liver, kidney or other organ is tough and leathery, and not until a microscopical examination is made do we realise how much fibrosis has taken place.

One thing seems quite clear, and that is that the motive which underlies this simplification of structure of the complex organs is one of sanitation. Just as after a destruction of tissue an attempt is made to repair the injury and to replace the lost part, so also the immigrant cells we see in the senile organ are evidently due to an attempt to clear away bad material and to reconstruct. It all indicates a return to an embryonic condition on the part of the higher order of cells, a horror of a physiological vacuum, and an attempt at replacement on the part of the lower kinds. It is a return to the methods of the embryo without the ability to produce the same result; and shows that healthy senile degeneration is not solely a passive process, but is characterised by a decided activity. But this activity does not now take the form of legitimate secretion, for it concerns the lower order of cells only, and is manifested mainly by proliferation. It is the activity of an inferior organisation, and on that account has in it elements of danger, for these more lowly types of cell are far more impulsive—more likely to break out into excesses—than are those more civilised.

In short, the main distinguishing feature of the tissue changes of second childhood as compared with those of first childhood is defective control. In early life there is a well-organised progression of cell-growth and development, leading exactly to the point required and no further. Every part is kept well under restraint, so that at no time, either during the progress of development or when it has attained its height, can it be said that there is any redundancy of tissue. This restraint of growth is one of the greatest marvels of animal life, and is none the less so because it is so patent and so commonplace that we do not realise its importance, or even its existence. It is as much a primitive attribute of the cell as is reproduction, contraction and nutrition, and, like them, reaches its highest development in the highest metazoa. The cells of a fungus are endowed with such

force of growth that a few of their spores sown beneath the paving stones of a town will entirely disarrange the work of the pavior. Yet these same delicate cells, which are capable of exerting so great pressure as to lift heavy stones, will spontaneously cease growing as soon as the fore-ordained size and shape of the fungus is completed. So in the same way the coercion of the foot of a Chinese woman is an affair of difficulty—of firm bandaging and intense pain. Yet this same growth when allowed absolute freedom will never overstep the limits which have been assigned as natural to the particular foot in question.

All this is true of life in general, but it is less true of senile than of juvenile life. In the tissues of the old there are evidences that growth control is much less perfect. Redundances are prone to occur, and some of these, as we shall presently see, arise in the whole of an organ simultaneously, perverting the natural senile changes into disease, one form of which is known as fibrosis ; or the redundancy may be limited to individual cells, and give rise to new growths or to cancers.

III

THE RELATIONS OF NORMAL DEVELOPMENT TO (1) THE CELL, (2) THE ORGAN, (3) THE COMPLEX ANIMAL

The cells of the body have an individual existence, co-operate together in communities or organs, and still further combine into groups of organs to constitute the complex animal. These three divisions correspond phylogenetically with the divisions of the animal kingdom into cells, primitive organisms, and complex organisms.

WE notice that under normal conditions cells behave differently, according to whether they act independently as units, or are assembled together for purposes of co-operation. That is to say, single cells or cell-groups must be distinguished from organs. There appears to be a genealogical precedent for this distinction. Every incident of ontogenetic development seems to be founded upon some prior incident of phylogenetic development. In fact, one of the most striking features of development, whether of the individual or of the species, is its intense and unbroken adherence to precedent. This is fully recognised when we are dealing with the facts of heredity. Nothing happens except as the expression of some pre-existing experience. Such a sequence is just as inevitable as that the upper stories of a house should not be suspended in the air, but should be built upon, and be influenced in shape and in character by, the lower stories. Hence, whenever we are at a loss to account for structures, functions, or expressions which do not seem relevant to the needs of an animal, we go back to some previous stage of evolution, and can generally account for them by reversion or atavism. For similar reasons, when we find that cells group themselves together for purposes of co-operation into organs, each of which behaves more or less independently of the somatic cells in general, we naturally look back for some precedent among the earlier facts of evolution. We notice that the rocking motion is soothing to the baby; that the boy delights in digging caves, in climbing trees, and in eating potatoes that have been taken half burnt and half raw from a bonfire; and that male youths find satisfaction in walking into

the country in droves carrying sticks. Until lately we have been content to regard these habits of the young human animal entirely from a utilitarian point of view. We have been far too familiar with them to see that they had a phylogenetic meaning. But now we know that the baby loves the to-and-fro movement of its cradle because it is reminiscent of a time when the human being was in the cradle-stage of its existence, when "hush-a-bye, baby, on the tree top" literally expressed the exact nature of the movement which was then natural to all stages of its existence. So also when we see boys enjoying the discomforts of an open-air fire, or young men out on their Sunday afternoon excursions, we think of the half-naked savages to whom a fire was a luxury, and of our semi-civilised and nomadic ancestors wandering with bows and spears over the face of the country.

After the same fashion, to understand the ways of our bodily organs it is not sufficient for us to look upon them simply from the point of view of utility alone. The individual man is constructed of cells or cell derivatives and of organs, not by blind chance, nor solely because such an arrangement of units is most convenient and suitable. If the protozoon be the primeval ancestor and prototype of all animals now living, there is quite as good reason for looking upon the primitive compound animal or first organism as the forerunner and pattern upon which such organs as the liver, kidneys, and brain have been constructed.* Just as the protozoa† have among them the beginning of metazoic combination, so also the earliest metazoa, such as the sponge and the sea anemone, have already started on that process of differentiation which will end in the complexity of the highest vertebrate. They are single organs in the sense that one organ obtrudes itself conspicuously in front of all the rest.

Every cell in the body may be said to lead a triple life. In the first place it lives an individual existence, for it retains to some extent those properties which are recognised to be the primitive characters of the independent unicellular animal. In the free cell they are well balanced—in keeping with the many-sidedness of the uses which are required of it. In the attached cell, which has lost its liberty and become subservient to the needs of other cells, one quality is exercised to the detriment of the remainder; but that it still possesses the old unicellular freedom in a dormant condition is proved by the way in which it awakes into activity

* We are informed that this view has already been set forth by Perrier, but we have been unable to obtain a copy of his book.

† See Ray Lankester, 'Monograph on the Infusoria,' p. 363.

when called upon by some physiological necessity. Thus the stagnant bone-cell, deeply embedded in its hard calcareous matrix, takes on the activity either of the destructive osteoclast or of the constructive osteoblast when some disaster has set it free to act for itself. In fact some of the ways of cells can apparently be explained only on the ground that they possess some primitive form of volition, or some faculty of the nature of a rudimentary intelligence, so original is their behaviour, so apt is the way in which they alter and adapt themselves to sudden emergencies. This is not only true of the phagocytic leucocyte, which migrates from its vessel in order to seize upon and destroy invading microbes or to carry away and expel a particle of dust, but is also true of the more highly organised epithelial cell, such as the special cell of the crypts of Lieberkuhn, as Dr. Woods Hutchinson has so well shown. These play an independent part, of which we have but little conception when we see them arranged in stiff, formal ranks in the hardened section prepared for the microscope. Dr. Woods Hutchinson compares their appearance under these circumstances with that of soldiers at drill, and their appearance during life with the same soldiers in the restrained activity and disorder of an engagement with the enemy.

And this brings us to the second of the triple lives which cells lead when aggregated together as organs. Though much of the work of the bone-cell, the intestinal cell, and other cells shows that they possess individual initiative, in other respects it seems equally clear that they are acting together in a collective or co-operative capacity. These two phases of their existence go on hand-in-hand at one and the same time, just as the bee works both for himself and for his hive, or as the common soldier fends both for himself and for his regiment.

Lastly, life in these two aspects, individual and collective, is subordinate to the needs of the larger organism of which the organ and the cell are members. The personal life of the soldier goes on at the same time with his life as the unit of a regiment, which, again, has to play both its individual part and to subordinate itself to the need of the army.

Trite as this subject must appear, it is very important, for upon the recognition of these three components of the body—the cell, the organ, and the complex animal—lies the very foundation of our subject. We cannot understand the differences which distinguish the developmental disease of the cell from those of the organ, nor, again, those which distinguish the organ from the whole individual, unless we realise the differences which characterise their healthy development.

We have now seen that evolution and development are interchangeable terms, and that the structure of any complex animal is founded upon phylogenetic precedents. First comes the *single cell*, comparable with the protozoon; then, neglecting the intermediate forms of life, the collection of cells together for mutual good into the compound animal or *organ*; and finally, the co-operation of numbers of such cells and organs into the *complex animal*.

This view of the basis of construction of the body is borne out both by the form and by the behaviour of organs. Organs vary in form as widely as do the early metazoa. Some, like the thyroid gland and the liver, are single, compact, self-contained masses; others, like the lymph organs, are multiple; some are in sheets, like the skin; others form tubes, like the intestines. But, despite their differences, they are based upon a common principle of form and use. This is well exemplified in the structure of such an organ as the kidney. The kidney is, in certain fundamental respects, a sponge-like structure. It is a collection of cells arranged on a frame-work, not of keratin, but of almost equally inert fibrous tissue. The collection of cells has an afferent stream of nutritive fluid, and an efferent flow of waste material. It is true that the functions are far more highly specialised in the organ than in the organism. Yet though they differ widely in detail they are alike in principle. And, what is still more notable, the organ is, to a certain extent, independent of the rest of the body. It is a community which grows, matures and decays, not always at the same time as the rest of the body, but at a time of its own. A kidney may, in short, be regarded as comparable with an organism of high development, one of a series which is shut off from the general somatic system by abrupt boundaries, working for and owing allegiance to the whole body, coming into touch with it when the general good is concerned, but in other respects living independently. Further, as we shall see later on, the kidney, like other organs, has its own diseases, limited within its own boundaries, and only affecting the rest of the body in a secondary manner by interfering with some work which is being carried out for the whole community. Hence, by reason of its specialised cellular structure, and its more or less independent life-history and pathology, we are justified in comparing an organ with a simple multicellular animal. It is a civilised compound animal, or organism, which has lost some measure of independence, and is anchored within the body; and, *vice versâ*, any primitive compound animal, like the sponge, we must look upon as an organ living a semi-savage and independent existence.

IV

THE RISE AND DECLINE OF NORMAL DEVELOPMENT

The origin of development is unknown, though we are acquainted with its effects. It is the outcome of the action of two opposing tendencies; one—heredity—conservative in nature, and consisting in the constant repetition of the same, or of similar characters; the other—variation—changeable, and either reactionary or progressive. The rate of development differs in different animals and in different organs of the same animal, and though continuous as a rule, is prone to be interrupted or rhythmic. These interruptions are in man shown in the so-called changes of life, in the monthly cycle, and in pregnancy, and are the reflex of seasonal and other external influences upon past development. Development may be prolonged by favourable circumstances or hastened by unfavourable, but death is inevitable.

WE must now refer to certain outstanding characters shown by development during its rise and decline. These are as follows:

(1) We know nothing of its *cause*. We are only acquainted with its effects, and with the influences by which it is guided or directed.

(2) One of its most peculiar features is its tendency to reproduce the characters of the parents. Certain facial appearances, mannerisms of writing and of speaking and so forth, are *inherited*; and one of the most important of these characters to be passed on is the duration of life.

(3) But this strong tendency towards monotony is opposed by the counterbalancing tendency to *variation*. Thus in a family in which the members usually mature early there may be one who does not attain puberty until much later, and this peculiarity may show itself without evident cause. On the other hand, in a long-lived family certain members may die from senile degeneration at unusually early ages, though they have lived careful lives.

These peculiarities may themselves be inherited, either by being transmitted from parent to offspring, or by occurring among brothers and sisters.

(4) Though heredity accounts for much in the development of an individual, yet his development is also influenced by his *surroundings*. If he live under depressing conditions, such as are implied in

poverty, in bad air, and in scanty and badly cooked food, or in dark valleys, marshes, or enervating climates, he will be prone to be backward in progressive development, to mature imperfectly and to degenerate early. For instance, it is well known that the hard, precarious lives and poor food of the Bosjesmans, of the Australian blacks, and of some negroes cause them to mature early, to become senile and to die from old age at a much earlier date than do those who enjoy opposite conditions of life.* Even in our own country, those who live well above the poverty line are better developed and live longer than do those whose livelihood is uncertain, who are engaged in dull, monotonous toil, or dwell in squalid, airless slums.

(5) The *rate* of development varies in different cases. One animal develops more quickly than another animal. The development of man is slower than that of the dog: the dog develops more slowly than the butterfly. As we have seen, the general rule is that the lower the rank in the animal kingdom, the faster is the development.

Not only do different animals vary in their rate of development, but the different organs of any particular animal also vary. Individual cells are used, cast out, or destroyed by phagocytes, and the work of the body goes on as if they had never existed; while many organs run their allotted course and decay long before the general life of the body is completed. The thymus gland dies in youth, the ovaries at about forty-eight, the testes often cease to be useful at or before sixty-five, and the bone-marrow and supra-renal capsules are practically extinct long before the rest of the body becomes valetudinarian. Death is rarely or never due to a general breakdown of all parts of the body, but is brought about by the earlier downfall of some one vital organ, such as the heart, kidneys, arteries, or brain.

(6) The course of development is *continuous*. Life, in the words of the Psalmist, is but a "day that is spent." First comes the dawn, when light is feeble; then the sun in its fulness, and, at the end of the day, the sunset, followed by the night. But there is an important discrepancy in this ancient simile, for while the light is grey in the morning and red in the evening, the glow of life is at the beginning, and its end is usually grey and colourless. Nevertheless the comparison is true in another respect, for development never stands still, but is progressive from beginning to end.

(7) Though progressive, development is broken or *interrupted* by

* The shortness of life is of course, in these cases, mainly racial, but even in that case the statement is correct, for this shortness is the accumulated result of centuries of environment.

periods of increasing progression or of increasing retrogression, alternating with periods of comparative rest. This rise and fall of development is but an example of that rhythmic movement, or periodicity, which seems to be an essential feature of the scheme of the universe. Life has its seasons, in common with the rest of organic creation. In the words of Cicero, "Nature conducts us, by a regular and insensible progression, through the different seasons of human life, to each of which she has annexed its proper and distinguishing characteristic."* Spring, summer, autumn, winter; the changes of the moon; day and night, are all alternations of rest and activity, and must, of necessity, leave their impress upon the plastic forms of life which grow under their influence, giving rise to periodical variations in animal development. In man these periods correspond in number with Shakespeare's seven ages, though the arrangement is different. They consist of foetal life, babyhood, childhood, youth, manhood, middle age, and old age. Each of these periods or stages is marked off from the preceding and succeeding stages by the epochs or changes of birth, puberty, and the menopause, or by some unnamed and less notable change, or climacteric. Some of these changes, though nameless, are almost as pronounced as those which are named. Thus there is an unnamed climacteric, dividing off the period of babyhood from that of childhood. It is often so conspicuous that mothers, usually very observant, are sometimes misled into supposing that it is the result of disease. They notice that the fat and placid *baby* has, within a few weeks, turned into a thin, restless *child*; and in spite of an improvement in appetite, the mother can only account for its altered condition by supposing that it is affected with worms, or with some wasting disease, such as diabetes or consumption. Then, again, the change that people pass through between middle and old age is occasionally so abrupt as to attract attention. Thus we meet some friend whom we have not seen for a year, and we notice that in the interval he has become an old man, though the rest of his family seem to have altered very little.

Most, if not all, of these stages and changes of development mark the rise or decline of some particular organ. Many of the peculiar features of babyhood are due to the growing importance of the thymus gland, and the change which takes place at the onset of childhood seems to have some relation to its degeneration. The period of childhood is dominated by the rapid development of the skeleton; that of youth or adolescence by the ripening of the sexual organs, and by a further and almost final spurt in the development

* 'De Senectute,' Melmoth's translation.

of the bones; and manhood by a universal adjustment or levelling-up all round. With middle age comes the beginning of the final downfall in the increase of fat, the degeneration of ears, eyes, hair, and teeth, and the decline in vigour of the sexual organs. In old age the degeneration extends to the skin, muscles, joints, bones, or brain.

But these are not the only interruptions in the course of healthy development. In the female the periods of youth and middle age are periodically broken into by the lesser event of menstruation, or by the more uncertain and far more pronounced events of pregnancy and the puerperal state. During pregnancy, and especially the first pregnancy, very striking changes take place. These at first seem to be mainly changes of nutrition, but a little closer observation shows that development is affected as well. It almost appears as if the mother to some extent takes a share in the rapid progress of nutrition, growth and development which goes on in her contained offspring. The situation reminds one of the reciprocating influence exercised by a planet and its satellites. The earth, for example, being by far the heavier body, exerts an attraction upon the moon. And this influence is so obvious and overwhelming that we are prone to forget that the moon, too, has a similar influence upon the earth. So also does it seem to be with the mother and child, and just as the lunar influence is more effective in its action upon some elements of the earth, of which the sea is the most obvious example, so also certain tissues of the mother are more influenced than others. The organs which undergo this sympathetic development in most pronounced degree are those concerned in the processes of reproduction and of foetal nutrition. The uterus, the breasts, the bones of the pelvis, all take a leap forward in their development. Changes go on in the bones, especially of the pelvis, which remind us of their state in babyhood. There is an increase in red marrow, sometimes so marked that the pressure gives rise to unpleasant aching, of the same nature and for the same reason as that which occurs in growing children, and as is known as "growing pain" (not the rheumatic form). The blood also is affected, the lymphocytes becoming more numerous,* as they are in the foetus. Hence, in regard both to the bone-marrow and to the blood, the change is in the direction of a return to a childish or to an embryonic condition. The same is perhaps true of the effect of pregnancy upon the tissues as a whole. For, as a rule, pregnant women undergo a marked alteration for the

* Moleschott, 'Wien. med. Woch.,' 1854, p. 113; also Cabot, 'Clinical Examination of the Blood,' p. 100.

better in their nutrition. There is a sense of improved health, and with it a corresponding fatness, which it may not be too fanciful to speak of as some slight return to the baby type, for both the maternal and the baby tissues seem to be of the more lymphatic or cellular order than are those of the non-pregnant adult. In healthy women nutrition is, as a rule, greatly improved during pregnancy, but falls off to some extent during lactation, a decline which is especially to be noticed if the baby be prematurely weaned. Cabot* has shown that the leucocytosis of pregnancy continues into the period of lactation.

Menstruation is in many respects a miniature child-birth, for there is reason to suppose that changes of nutrition and of development go on during this period similar to those which take place during pregnancy and lactation. But whatever may be said on this score, there can be no doubt that menstruation is also a critical time in female life, and that it exercises an undoubted influence upon the whole body. Pigmentary changes and vascular changes are sure indications of some interference with nutrition, and through nutrition in all probability with development as well.

Dr. Engelmann,† as the result of an investigation of the menstrual condition of 4873 American girls, found that, generally speaking, there is one or two days of increased energy and capacity for work prior to the flow, followed by a period of moderate lassitude, and feeling of unfitness during the flow.

Dr. Helen MacMurchy, of Toronto,‡ who quotes the observations of Dr. Jacobi§ and others, and gives the results of her own investigations into the physiological phenomena of menstruation, arrives at the conclusion that there is a maximum excretion of urea, and a rise of temperature before, and a rapid fall during the "period," until the minimum is reached shortly afterwards. This wave coincides with a corresponding rise and decline of arterial tension. Some of the facts elicited by Dr. MacMurchy "seem to indicate a lessened power of resistance, or a greater liability to infection" during the flow.

Women often express themselves as feeling at their best during the week before menstruation sets in, but a rapid decline of this sense of well-being ensues after the "period" has started, and continues for about a week.

* Cabot, 'Clinical Examination of the Blood,' 10th edition, 1903, p. 100.

† 'Medical Record,' December 1st, 1900.

‡ 'The Lancet,' 1891, vol. ii, p. 909.

§ 'Boylston Prize Essay,' Harvard University, 1886.

It has just been said that menstruation is a childbirth in miniature. It would be more exact to reverse the simile, for, as a matter of fact, there is every reason to believe that the process of child-bearing and the subsequent events are, so far as the mother is concerned, no more than exaggerations of the menstrual period. It would be strange if it were not so, for with a suitable mechanism already at hand it would be contrary to all natural custom for it to remain unutilised. The fecundated ovum, cast, as it were, haphazard into the menstrual cycle, prolongs the next pre-menstrual epoch during an interval of nine months. This pre-menstrual time is, as we have just seen, a time of well-being—of improved nutrition and of increased capacity for resisting bacterial disease. No period in the life of a woman could be more fitting than this, if prolonged and magnified, for the bearing of offspring. This, therefore, is almost undoubtedly the real explanation of the improved nutrition of the mother during pregnancy. The alteration springs from herself, but is induced by her fœtus, acting in all probability by a process of rapid adaptation or correlation. At the end of the ninth month the suspended menstrual period descends in the act of childbirth, and is prolonged until the products of conception are all cleared away. This exaggerated menstruation of childbirth is, therefore, like the time of actual menstruation, one of comparative depression.

The period of pregnancy and of the puerperal state is, therefore, a true physiological epoch; or rather, like that of menstruation, it is a double epoch, in which the pendulum swings first in one direction and then in the other. Moreover, it is an epoch of some magnitude, one in which serious pathological changes are likely to take place.

This view of the relation between menstruation and the pre-menstrual state on the one hand, and childbirth and the pregnant state on the other, has, we find, already been pointed out by Dr. Keller.*

(8) Development never lasts indefinitely; the great final change may be hastened or postponed to the extent of a few years at the outside. It may be delayed by suitable and sufficient food, clean air, effective drainage and good hygiene generally. A contented mind, bright sunshine, pleasant society, and temperance in eating and drinking no doubt contribute to the same end. On the other hand, defective hygienic conditions, depressing surroundings, or poor and insufficient food tend to bring about premature old age. But, under the best possible conditions, death is inevitable,

* 'Journ. de Gynec. et de Obstét.,' vol. lv, May, 1901.

and no one has yet discovered any drug which will retard the final breakdown, even for a month.

But these are not the only factors which influence development. Lack of the necessities of life, as well as excesses of all kinds, are detrimental, and tend to hinder development in its rising stages, and to hasten it in its falling stages. Thus, a defective food supply, too little sleep, insufficient clothing, lack of exercise, are all obstacles to a proper development. Moreover, it is to be observed that privations are relatively of more consequence in the earlier years, at a time when the processes of life are active, and consequently most in need of support. Excesses, on the other hand, are, as a rule, more harmful in middle or old age, because the functions have then sobered down to a steady pace, which requires no forcing. The evils of a scarcity of food are most felt in childhood; whereas in old age it is no great hardship to fast, and such fasting seems to have but little effect in shortening life. Excessive eating is a venial offence in youth, but in old age the penalty of gluttony is death. Luigi Carnaro* and Professor Humphry† are in agreement upon this point, that after forty, or thereabouts, an abstemious life is most conducive to an advanced old age. As it is with food, so is it with drink, with sexual congress, and perhaps with exercise and work. Excess in any of these directions is detrimental to development in its earlier phases and tends to delay it, but is even more powerful in hastening senility in the middle-aged and old.

The particular forms of excess which are most striking are, as may be supposed, those which act in a concentrated form in a short space of time. This is best shown in the case of the depressing emotions. There are many instances on record of the obviously ageing effect of intense grief, anxiety, fear, or terror, when brought to bear upon a susceptible individual under favourable circumstances. Wanley‡ quotes among other examples one given by Schenk, in which a nobleman "was cast into prison, and on the morrow after he was to lose his head. He passes that night in such fearful apprehensions of death, that on the morrow, Cæsar sitting on the Tribunal, he appeared so unlike himself, that he was known to none that were present, no, not the Emperor himself. All the comeliness and beauty of his face was vanished; his countenance was grown like that of another man; his hair and beard turned grey; and in all respects so changed that the Emperor suspected some counterfeit

* George Herbert's Trans.

† 'Old Age,' Sir George Murray Humphry.

‡ 'A General History of Man,' 1788, p. 126.

was substituted in his room.” This is but an extreme and, perhaps, somewhat apocryphal instance of a well-recognised sequence of cause and effect. Yet we all recognise that happiness, joy, laughter, contentment conduce to fatness and long life, and that *per contra* unhappiness, grief, discontent, anger, jealousy, tend to produce a sour physiognomy, a lean body, and a short life.

Further, it is probable that when a number of depressing conditions act together or in conjunction with over-fatigue their influence is greater than when they act alone. Thus it has again and again been noticed by military authorities that troops engaged in the pursuit of a retreating army are far better able to endure hardship than are the troops they are pursuing, who, in addition to the physical fatigue of forced marches, are depressed with the sense of defeat, and with the fear of their pursuers. Napier, in his ‘History of the Peninsular War,’ draws a vivid picture of the horrors incidental to the retreat of Sir John Moore to Corunna, and of the indignation expressed by the public at home when the ragged, emaciated victims of the retreat were afterwards landed in our southern ports. Yet the French soldiers were hurried forward with even greater expedition than the English in the attempt to cut off the English retreat, but we hear nothing of the effects of privation and fatigue upon them.

During the Civil War in America the Southern States subjected their prisoners to a combination of depressing conditions. The food was badly cooked, insufficient, often rotten, and of poor quality, and the men were too much exposed to the cold in winter and the heat in summer. The camp was crowded, and its sanitation deplorable. Above all there was no work to be done, so that the men spent their days in idleness, brooding over the miseries of their situation. As a consequence they died like flies, and the few who survived the war returned home more dead than alive. Walt Whitman, who had himself acted as a sick visitor and nurse in the army hospitals during the hostilities and saw these prisoners on their return, was horrified at their appearance. No one who knows his writings will be likely to forget his description of their condition. He states that over 50,000 men died in the Southern prisons, and that “the dead there are not to be pitied as much as some of the living that come from there—if they can be call’d living—many of them are mentally imbecile, and will never recuperate.”*

Conditions capable of producing such dreadful misery and such

* ‘Specimen Days in America,’ by Walt Whitman.

an appalling death-rate must tend to shorten life even though they exist but for a season and the victim survives. The same must, of course, be equally true of smallpox, typhoid, the plague, or, indeed, of any other debilitating disease. Though we apparently have no clear evidence upon this subject, such as would be furnished by statistics, yet it is hardly possible to doubt that such devitalising conditions promote the onset of senile decay.

We have now seen that development and degeneration are two phases of one process, and that degeneration is but a retrogression, or return to an earlier form of development. Development (including degeneration) is (1) without visible cause; (2) its characters are hereditary, (3) but show a tendency to variation, some of these variations themselves being hereditary; (4) it is influenced for the worse by depressing conditions, and for the better by good hygienic conditions; (5) its rate varies in different beings and in different organs; (6) its course is progressive, (7) but is interrupted, or broken up, by intermissions, including those due to sex; (8) though retrogressive development may be delayed, it does not continue for ever, but always comes to an end within certain ill-defined limits of time.

V

DISORDERS OF GROWTH AND DEVELOPMENT

Classification : The trinity of nutrition, growth and development, united in health, are separated by disease. Each may be either morbidly defective or excessive. The morbid defects and excesses of growth and of development undergo considerable modification according as they affect isolated cells, cell communities (organs), or co-ordinated collections of organs (complex organisms).

GROWTH, development, and nutrition were compared in the beginning of the second chapter with the three colours of the spectrum, which are so blended together as to appear as one. But with the help of a prism white light can be split up into its constituent colours, and so also may growth, development, and nutrition be separated from one another, and the prism which separates them is disease. This is well exemplified in some of the higher plants. The growth of trees is normally so precise, conforming so closely each to its own particular type, that we can at once say from the general configuration, from the direction of its branches, and the shape of its leaves, whether a given tree is a birch, an oak, or an ash. But let disease affect the tree, let its buds be attacked by some insect pest, and this orderly arrangement is destroyed. Growth becomes overgrowth, or undergrowth; nutrition becomes defective or excessive; development, exaggerated or retarded. Overgrowth takes the form of bosses or tumours, and the branches which spring from them are small and irregular. In some parts the leaves appear a week or two before their time, while in others foliation is delayed, and the part becomes more vulnerable to the attacks of fungi.

A similar sequence of events takes place in animals under similar circumstances. If, for example, such a fungus as that of actinomycosis gain lodgment in the body, overgrowth of a low, embryonic type of cell takes place, with undergrowth of those peculiar to the part affected, and the new tissue so formed is prone to break down into an abscess. In short, a boss or tumour is formed, and in this tumour, or on its outskirts, the three processes of growth, development, and nutrition tend to part company.

Disorder in these cases takes the form of excess or defect. Not only are growth, development, and nutrition subject to these forms of disorder, but it must be self-evident that every function of the body, every attribute, every cell, every organ, every complex individual is liable to become disordered after the same fashion. Hence, we may have morbid excesses or defects of temperature, of assimilation, of secretion, of mental conditions. Anuria and polyuria, anorexia and bulimia, constipation and diarrhœa, apathy and exaltation, melancholia and mania are all examples of disorder by excess or defect. Metabolism, arterial tension, the beat of the heart are all liable to preternatural increase or decrease.

In the same way, when the trinity of growth, development, and nutrition is split into its elements by disease, each of the three may stand out far too conspicuously from its fellows by reason of abnormal excess or defect.

Nutrition.

Defective nutrition is indicated by undue vulnerability to the attacks of micro-organisms. Ulceration or suppuration occurs too readily. **Excessive nutrition** shows itself in coarse or redundant growth, as *e. g.* in the growth of hair on the outskirts of ulcers, or of fat, blood, and tissue generally in plethora.

Growth: Defective and Excessive.

Primary defects and excesses of growth may be naturally divided into three classes, according as the part affected is—

- (A) a cell or cell group (tissue),
- (B) a cell community (organ), or
- (C) the complex body as a whole.

It is of great importance that these should in each case be distinguished from the corresponding anomalies of development.

(A) 1. When **cells**, singly or in groups, are affected with **overgrowth**, the result is known as an innocent tumour or new growth. Lipomata, enchondromata, osteomata and adenomata are no more than outgrowths of fat, cartilage, bone or gland-tissue respectively.

Development and nutrition are also affected to some extent, it is true, but innocent tumours are primarily and essentially excesses of growth. They are the mountains of the body in which the tissue strata are upheaved and distorted, but are not to any great extent altered in quality.

2. Primary **undergrowth of cells or cell groups** is an academic

disorder of no importance. The cells of an organ are so plentiful that the loss of a few of them is not noticed.

(B) 1. Primary **overgrowth of cell communities or organs** accounts for such borderland conditions as general muscular "hypertrophy," and simple idiopathic enlargement of the liver, kidneys, lungs, and other organs. Such enlargement may or may not give rise to pathological symptoms, according to the nature of the organ affected. Thus, simple overgrowth of the muscles or fat may do no more than increase strength or weight, though the latter may produce pathological consequences by embarrassing the heart, or by impeding the function of other organs. On the other hand, simple overgrowth of the thyroid gland, by increasing the activity of that organ, may produce severe, and even fatal, consequences. Spontaneous overgrowth of the thymus gland and of other lymphatic structures also occurs, and is one of the causes of sudden death in children. Simple overgrowth of the skeleton may possibly account for one form of gigantism, since some very tall men are obviously provided with skeletons which have outgrown their muscles and other soft tissues. In the same way the genius, or intellectual giant, like Newton, Bacon, Cuvier or Shakespeare, who possesses an intellect which towers high above that of the average man, is, in all probability, an instance of overgrowth of the brain. Gladstone is another example of excessive brain growth, for his head was not only so extraordinarily big that he required a hat to be specially made for him, but it is also stated on good authority that it behaved abnormally by undergoing marked increase in size long after he had reached maturity.

Of course in many cases increased growth may be largely due to the cultivation of function, but we must all recognise that apart from that, each organ of each individual has its own standard of growth, and that no amount of exercise, however judiciously used, will produce any great extension of size beyond it. The career of an organ is in one respect like a game of whist. The success of such a game is in part the result of skill, but is to a far greater extent due to the nature of the cards which fortune has put into the hands of the player. His cards may be so bad that, play as he may, he cannot do well; or, at the other extreme, he may have a hand so full of trumps or of court cards that crass stupidity on his part can alone prevent him from winning the game.

It is probable that no organ in the body escapes liability to spontaneous, freakish overgrowth. For example, it is known that at *post-mortem* examinations the liver is sometimes preternaturally large without being diseased, or one lobe alone may be so affected.

We have known one instance where such an outgrowth was mistaken for a tumour and was removed by operation, with a disastrous result. The lungs may apparently be affected in the same way. We once saw with Mr. Timberg, of Reading, a gentleman whose chest was so big that it projected in front of him like the pouch of a pointer pigeon. This unfortunate man could not escape the persecution either of those who knew him or of those who did not know him. His friends accused him of vanity in over-padding his chest, strangers turned round to stare at him as he walked, and the street boys openly made fun of him. Examination of his chest revealed nothing amiss except that his lungs seemed excessively big. There was no sign of emphysema.

Every organ in the body is liable to a similar excess. In one, it may, as with Cyrano de Bergerac, take the form of a conspicuous nose; in another of uncommonly big feet or of distressingly large ears. In one case the enlargement is of an external organ; in another of an internal organ, such as the uterus, the heart or the colon.

It is possible to distinguish *two kinds of overgrowth*. The first is to be noticed during progressive development, and seems to consist in an exaggeration of the impulse of growth which naturally occurs at that time of life. A good example is to be met with in the shape of that form of parenchymatous growth which gives rise to Graves's disease in young women. The other kind of overgrowth occurs later on in the life-history of the gland, at a time when its development is on the wane, and is a sign of commencing degeneration. It is this form which sometimes gives rise to projection of the thyroid gland in middle-aged women. It is less likely to lead to excess of function, and is often associated with adenomata or other forms of single cell overgrowth. Other examples will come before us later on when the diseases of organs are systematically dealt with.

2. **Primary undergrowth of organs.**—This, in practice, is often not to be distinguished from defective development. At the same time it is positive that hypoplasia, microsomia, or dwarfism of organs does actually occur, and that it is distinct from defective development or infantilism. In such cases an organ or part of an organ prematurely stops growing, and is characterised by its smallness of size, though its development seems to be perfect.

A good example of simple hypoplasia of many of the viscera, occurring in a woman of average general development, is recorded by Dr. Martin.*

(C) 1. **Primary overgrowth of the whole body** is gigantism. It

* 'Brit. Med. Journ.,' 1906, vol. i, p. 1379.

is now recognised that many giants owe their stature to acromegaly, but all giants are not acromegalic. Some are of good all-round development, are strong, and show no evidence of disease, but are of fair proportions, and live to an average length of life. Robert Hales, the Norfolk giant, and Bates, the Virginian giant, together with his wife, are cases in point. In photographs of them standing alone, without any chair or other object to show their proportions, they look like people of ordinary height. They seem to be instances of growth carried to excess. At the same time such extreme instances of overgrowth as that of Hales and of the Bates's must be regarded with suspicion, for extremes either on the one side or on the other are almost necessarily due to disease. Nevertheless, we must recognise the existence of men and women with excessive stature, who, apart from their abnormal size, show no sign of disease.

2. After the same manner we meet with *dwarfs*, who are merely miniature men and women. They show no indication of backward development, of disproportion, or of disease. A skeleton given by the late Professor Sir G. M. Humphry to the Cambridge Pathological Museum seems to have belonged to a dwarf of this type. It is fully developed, and appears to be normal in every respect save in respect to size. But it must be noted that it was obtained in Paris, and was without history, so that it may possibly be the skeleton of an Akka, a Bosjesman, or some other racial dwarf. We have measured and otherwise examined an English female dwarf of twenty-two years of age who was only 129·5 cm. in height, who was free from all signs of abnormality in other respects, and whose development was apparently quite up to the average.

Development: Defective and Premature.

The way has now been cleared for the consideration of the primary defects and excesses of (the rate of) *development*. These also may be divided into three classes according as they affect—(A) isolated cells, (B) cell communities (organs), or (C) the body as a whole.

(A) 1. **Primary defects of development of CELLS or cell groups.**—According to Cohnheim's theory, cells whose development has been unnaturally impeded or stopped may remain dormant in the body for long periods of time, and may then grow in a very active and aggressive manner to form carcinomata or sarcomata.

2. **Premature senility of CELLS or cell groups.**—The same result—malignant growth—may occur if well-developed cells of any part undergo premature degeneration, *i.e.* retrogression to a primitive type.

It is too often assumed that degeneration consists in the appearance of granular, amyloid, or fatty changes only. These are not the only evidences of the cell being effete, or senile. Nuclear changes, increase or decrease in size, poorness in chromatin, loss of phagocytic power, and the appearance of newly formed embryonic cells, or reversion to an embryonic type, are equally expressive of the same event. Old age, as we have seen, implies second childhood; and is expressed quite as much by an abortive rejuvenescence as by molecular decay. This applies to the ultimate cell elements or groups of cells as well as to organs and to the body as a whole. One of the chief characters of embryonic cells is their power of vigorous growth. By virtue of *their low organisation* such cells increase with great rapidity, and in this, as in other respects, differ so markedly from the more highly civilised tissues around them that, when in the adult body, they become, to all intents, parasitic. If the innocent tumour be due to excessive cell-growth, and may be compared to a mountain, the malignant tumour is the volcano, for its structure is different, more primitive, from that of the strata upon which it grows, though it is composed of the same elements.

(B) 1 and 2. **Defective development and premature senility of ORGANS.**—Every organ, like every cell, is developed from simple undifferentiated cells, and is fated to reach the climax of its development, and, if life continue to its normal end, to undergo senile decay. Such cell communities have their own special development, special structure, and special uses; are liable to fall into extravagances of development—perversions by excess or by defect—and these differ in character from those which distinguish the degeneration of cells. They differ, in fact, in a way and to a degree similar to those which distinguish the cells from the organ.

Such perversions must, to a large extent, be tinged with the characters of normal development. If the healthy organ attain a certain size, then the organ which stops short in its development will be smaller; while the organ which undergoes premature old age will be so filled out with an excessive growth of embryonic tissue that it will be larger, or at any rate will contain more than the normal number of cells. So is it with functional characters. These also will in most if not in all cases be present in a diminished or exaggerated degree, and at the same time will be more or less warped or altered. They will be affected both in quantity and in quality. Changes which go on in healthy old age are very slight in degree because vitality is everywhere on the wane and death soon puts an end to all things. But abnormal old age, occurring

in an organ of a body which is still young, may be expected to produce far more effect than normal senility can do. Retrograde changes in the higher types of cells will then be excessive, while those incursions of embryonic cells which are also characteristic of senility will have time and opportunity to produce accumulations of extraordinary degree. Further, we shall expect to find imitations and exaggerations of those functional features which we have seen characterise healthy development and decay. Thus we should expect that presenilities will not only be more irregular in their appearance than are the changes of healthy old age, but will also continue to a greater degree; they will be exaggerated into the symptoms of disease. We also anticipate that each epoch of life will have its special diseases, each consisting of an exaggeration of those developmental changes which are natural to it. In other words, the normal tide of development becomes a flood or a storm. Hence, while the climacteric of puberty gives rise to Graves's disease, osteomalacia and the insanities of adolescence, the climacteric of the menopause is the starting-point of myxœdema, osteomalacia, osteitis deformans, the carcinomata, and of climacteric insanity. So also is it with the second childhood. The tissues of the old have again become more vulnerable, as they were in early life, and the individual is once more liable to childish diseases, to thrush, bronchitis, chilblains, indigestion, eczema, pneumonia, scrofula. In the evening of life the tissues tend to break out into various irregularities of growth, into warts, acne, nævi, moles, freckles, just as they did near the dawn of development; and delirium is a frequent concomitant of the old man's disease, just as it is of the baby's. Certain physiological processes tend to increase, and to merge into the pathological, so that no one can say where the physiological ends and the pathological begins. Thus the bowed figure of the decrepit old man seems to be the prototype of osteomalacia and osteitis deformans; and the same may be said in effect of the fibrous liver and kidneys of the aged in their relation to true cirrhosis and Bright's disease, of the shaking limbs to paralysis agitans, or of mental second childhood to senile dementia.

(C) 1 and 2. *Defective development and premature senility of MAN as a whole.*—These two conditions, respectively known as general infantilism and as general senilism, need no further comment here. They will receive particular attention later on.

Let us now see how these disorders of growth and of development may be sifted out from other diseases, and how their course, symptoms and anatomy bear out the forecast which has just been given.

VI

THE SEPARATION OF THE DISORDERS OF GROWTH AND OF DEVELOPMENT FROM OTHER DISEASES

Disease necessarily falls into one of three groups : to wit (1) that of external origin ; (2) of internal origin ; or (3) of both.

I. Diseases of Extrinsic Origin : Of all external disease agents the most important are the toxins. These may either be manufactured within the body or outside. The terms toxin, drug, remedy, and disease-producer are interchangeable. The toxins have an important influence upon growth and development. Amongst the most important are alcohol (the toxin of the yeast microphyte), syphilis, and lead.

II. Diseases of Intrinsic Origin : Pre-natal malformations and tumours are the principal members of this group, but with increasing knowledge definite causes for pre-natal malformations become more and more evident. Chief among these are lead and alcohol and the toxins of tubercle and syphilis. The innocent tumours are cryptogenous, sporadic, with occasional endemic tendencies, sometimes hereditary, progressive, and incurable by drugs. The cancers are, in addition, rhythmic or intermittent in their course, and malignant or lethal. The innocent tumours are growths, the malignant, degenerations.

III. Diseases of Mixed Intrinsic and Extrinsic Origin : These are for the most part certain disorders of growth or development, such as chronic Bright's disease, cirrhosis of the liver, goitre, leukaemia, etc. Like the intrinsic, they are divided into disorders of *growth* and disorders of *development*, or degenerations. The former are sporadic, occasionally endemic, sometimes hereditary and progressive, but interrupted in their course, and incurable by drugs. The disorders of development are in addition malignant or lethal.

Disease in General.

WHEN reduced to its simplest terms disease is dis-ease, or lack of ease ; and disorder is dis-order, or lack of order. On inquiring into the causes of these derangements of ease and of order, we find that though we seem to have a multiplicity of different factors to deal with, yet they are in reality of two kinds only. There is no disease in existence which is not ultimately due either to the action of some outside influence upon the body, or to some influence which proceeds from the body itself. All diseases are either of extrinsic origin (ectogenetic) or intrinsic (endogenetic), and due to some primary perversion of cell structure or function. As a corollary to this statement it is, of course, possible for both sets of causes to come

into action, either at the same time or one after the other. Hence any disease may be placed in one of three great groups, according to whether it has its origin in external or internal causes, or in both.

In order to clear the ground for the consideration of the endogenous diseases, it is necessary to have a very precise understanding of what we mean by diseases of extrinsic origin.

I. Diseases of Extrinsic Origin.

The ectogenetic diseases constitute a very wide group, some of them, indeed, being not familiarly regarded as diseases at all. Thus we must include among them such gross lesions as those which are produced by knives, bullets, or falls from a height; and at the other end of the scale, such intangible affections as those which result from too great heat or cold, from X or radium rays, and from electric discharges. Still more subtle as disease producers belonging to this same group are those influences which give rise to mental shock or emotional disturbances. And it is important to realise that, however occult the working of these causes may be, their effects are sometimes quite as potent as the poisons which give rise to, say, scarlet or enteric fever. They may, indeed, with truth be described as psychical toxins.

Of the toxic effect of strong emotional shocks we have lately witnessed a painful and dramatic example:

A girl, aged 16 years, had been brought up by a lady as her own daughter, though in reality the mother was still alive. This mother was an inveterate drunkard, of whose existence the foster-mother had succeeded in keeping the girl ignorant by means of occasional doles of money. But, in course of time, the increasing poverty of the foster-mother prevented her paying the usual bribe, and one day the girl was suddenly brought face to face with a coarse and bloated virago, repulsively drunk and abusive, who announced that she was the mother, and had come to fetch her away. Though the girl refused to leave her foster-mother, she was so overcome that the result was as if she were seized with a severe illness. She had to take to her bed, the tongue became furred, the skin sallow, the urine thick; and for the time being she lost all interest in life, ceased to care for her food, and became thin, weak, and anæmic. But after about three weeks she gradually recovered, and is now, some two months after her shock, slowly resuming the plumpness and flow of spirits for which she was at one time distinguished.

Perhaps the most important of the disease-producers of the ecto-genetic group are living organisms. A few of these are of the animal kingdom, and include such widely different parasites as the flea, the itch insect, the tape-worm, the malarial protozoon. But by far the most important are the toxins or poisons. These may be divided into two kinds; (1) those formed within the body, and (2) those formed outside the body and subsequently introduced.

(1) Of the poisons formed within the body the great majority are of bacterial origin. They vary widely in toxicity, some, like the organisms of chickenpox and German measles, having slight toxic power; others, and among them those of smallpox and plague, having intoxicating properties of great virulence. In all cases the toxins produced by the bacterium seem to be a bye-product of its action upon the substance in which it lives. If not actually an excretion it is of the nature of an excretion, and its baneful effect seems to be that which is common, in greater or less degree, to excretions in general. And just as our own excretions become the instruments of destruction if retained in our vicinity, so there is reason to believe that the microbial toxins, or excretions, are not only poisonous to the animal in which they live, but are inimical to the microbes themselves, so that when the toxin has reached a certain strength it tends automatically to limit or suppress the further growth of the microphyte producing it.

(2) Many toxins are manufactured, not within, but outside the body, and are subsequently introduced. One of the microbial invasions (that of enteric fever) takes place from the point of vantage of the intestinal canal. In some diseases the microbes apparently remain in that canal, so that their toxins alone reach the true interior of the body. This seems to be the case with some diarrhoeal diseases. But occasionally disease is set up by the introduction of toxins which have been manufactured away from the body, as, for example, when the bacteria which exist in decomposing meat set up so-called ptomaine poisoning.

Of a similar nature are the intoxications produced by forms of vegetable life other than bacteria. Thus when the deadly amanita, or other toxic fungus, is swallowed, its poison is exactly comparable with the toxin produced by the bacterial fungi. Though in the one case the poison is absorbed in one potent dose, and in the other recurring doses are supplied by the living organisms flourishing in the body, the difference is a mere detail. There is no fundamental distinction between them.

So also, to carry the argument a little further, the strychnine,

morphine, and atropine produced by other and higher members of the vegetable kingdom are all on a par with the bacterial toxins. Although produced by the plant, and stored up in certain of its cells, they are just as truly excreted as a bye-product from the surrounding air and soil as are the toxins of enteric fever excreted from the air and soil of the body which harbours its bacillus.

But no one can draw a line between the alkaloids or glucosides formed by the toad-stool, poppy, vomica nut, or deadly nightshade, and those formed by the willow, the castor-oil plant, or those medicinal agents which are turned out as artificial products of the laboratory, in the form of the salicylates, antipyrin, phenacetin, and phenol. All must be grouped together as belonging to the class of toxins, drugs, or remedies.

We must, therefore, come to the conclusion that a drug for the remedy of disease and disease itself, or rather the cause of disease, are one and the same thing. Whether any particular substance shall act as the one or as the other is merely a question of application. We all recognise that when administering a drug for the relief or cure of illness we are, generally speaking, introducing that which produces its own array of symptoms. And no one who has had occasion to treat syphilis with mercury, psoriasis with arsenic, biliary colic with opium, acute rheumatism with salicylates, or any illness with alcohol, can have failed to notice that the symptoms produced by the drug are as much in need of observation as are the symptoms against which the drug is directed.

As disease is no more than the disorder of the mechanism of the body or mind, so any substance which is capable of disturbing function is a possible cause of disease; and any substance which can cause disease is *ipso facto* a potential remedy, for the very property of upsetting function implies the possibility of restoring it when it has once been upset. The one action is not only not incompatible with the other, but is its necessary consequence. One of the most familiar instances is that of castor-oil, which gives rise to a temporary diarrhœa, and so acts as an intestinal toxin to those who are healthy. But the same substance used for the disorder of the opposite nature is a remedy. It neutralises constipation. So also lead, atropine, morphine produce the diseases respectively known as plumbism, atropism, and morphism, and relieve or cure other morbid conditions. The words "disease" and "disorder" are associated with pain, discomfort, or, at any rate, with that which is unpleasant; but such a conception is by no means essential, for some diseases are pleasurable. The warm glow of some fevers may be distinctly

pleasant, especially if it follow a rigor; the subject of acute delirium may be in an ecstasy of joy, and no one less deserves to be pitied than the patient with delusional insanity of the grandiose type. So far as he himself is concerned, he is, it may be, a king, and, moreover, a king who realises and appreciates his exalted position with far greater intensity and conviction than any real king ever did. Morphia and cannabis indica, again, give rise to intoxication so far from painful that they are deliberately used for the sake of pleasure alone.

Among the most important of these toxins is alcohol. Alcohol is virtually the excretion of the yeast plant, which again is a fungus, differing from the bacteria only in certain unimportant particulars. It is, to all intents, a big saprophytic bacterium, whose presence in a suitable medium results in its multiplication and in the formation of a toxin.

The fact is not sufficiently taken into consideration that this alcohol, the toxin of yeast, is one of a group of drugs of which morphia, chloroform, and ether are also members. All of them are characterised by their narcotic properties, by acting as stimulants and by having certain other features in common.

Taken into the blood in sufficient quantity any one of this group will give rise to a set of symptoms to which the term "intoxication" was given long before it was applied to the effects produced by toxins in general. Moreover, the word "fermentation," which has so long been associated with the growth of the yeast microbe, has also been extensively used for the essentially similar process which goes on in the blood when it forms the pabulum or wort for the growth and multiplication of the microbes of smallpox and other zymotic diseases (*Ζυμοτικός*, causing to ferment, from *Ζύμη*, leaven).

Further, the identity of their action with that commonly known as disease is proved by the inhibitory effect of concentrated alcohol upon the growth of the yeast plant, by the way in which they establish an immunity against themselves, and by the effects of their habitual use upon general health and longevity.

In the manufacture of alcohol from yeast, so soon as the toxin reaches a certain proportion its production is first delayed, and then, as the quantity goes up, gradually ceases. This seems analogous with the automatic cessation of the production of disease toxins in the blood under similar circumstances.

Again, the toxin of wine resembles the toxins of many diseases in increasing the resisting properties of the tissues against itself. So conspicuous is this that a state of immunity is at last acquired by

some seasoned toppers, so perfect that they are apparently unable to drink enough alcohol to become intoxicated, provided it be taken in a diluted form. This alcohol immunity extends in greater or less degree to other narcotics of the alcohol group, but apparently does not embrace drugs or diseases belonging to a different class. Thus anaesthetists find that a patient accustomed to heavy libations of alcohol requires larger doses of ether or chloroform in order to produce unconsciousness (drunkenness), and the stage of excitement (inebriation) is often very marked and prolonged. This reciprocating immunity is to be noticed in the case of morphia. We have seen a morphia *habitué*, in the habit of taking 36 grains of the toxin each day, who could not render himself drunk with alcohol, even if he swallowed a couple of bottles of raw spirit. He seemed to be equally invulnerable to both drugs.

It is recognised that immunity to alcohol and to certain disease toxins (*e. g.* of measles, tubercle) is low in (1) savages, (2) the feeble-minded, (3) those depressed by overwork and privation.

Nothing is more remarkable than the breakdown of alcohol-immunity occasionally to be observed in seasoned toppers. This is exactly comparable with the similar loss of immunity to streptococcic and other intoxications occasionally observed in the subjects of carbuncle, furunculosis, cystitis and similar microbial invasions.

But the point of most importance to us is the effect of alcohol upon health in general, and upon certain organs and tissues of the body in particular. That the effect of large and habitual doses of alcohol is inimical to health cannot be gainsaid, for it is a matter of common observation. But in regard to small quantities much difference of view still exists. It is the opinion of most people that, however pernicious the excessive use of this drug may be, its moderate use is not harmful, but may, on the contrary, be of decided benefit, promoting the happiness or enjoyment of the individual, lubricating social machinery, and adding, rather than subtracting, from the number of his days.

It is conceivable that a drug may act with deadly effect in large doses and do positive good in small. In order to test this point it is requisite that we should understand something of the action of alcohol, and find if there be any statistics to afford help on the subject. But these questions must be entered upon in a coming chapter. All that can now be said is that alcohol taken in large quantities undoubtedly disorders the body. Moreover, if it be of any value as a true drug it must necessarily be a disturber of normal function, no matter whether its effects be pleasurable or the reverse.

However slight the effects may be, if of the nature of an interference with the normal balance of the functions of the body they are disease effects—not physiological, but pathological.

Whatever may be said on the subject, there can be no doubt that in alcohol we have an excellent example of the way in which some substances of ectogenetic origin both produce disease and remedy disease, are at the same time toxins, and the agents of pleasure and conviviality.

The generalisation to which all this leads is, that there is a great group of diseases which result from the action of agents which have found their way, or have been deliberately introduced, into the body from some external source, and that this group is of very wide extent, embracing not only many of those pathological states ordinarily known as diseases, but also those which result from the administration of drugs.

II. Diseases of Intrinsic Origin.

After putting on one side all diseases due to agents introduced into the body from without there still remain a certain number which cannot be attributed to any external cause, but owe their origin to the action of some unknown influence proceeding from within. Among the chief of these are the pre-natal malformations, and the tumours, innocent and malignant.

Pre-natal Malformations.

The causes of most pre-natal malformations are, as yet, hopelessly beyond our knowledge. This is largely due to the fact that the flaw in the process of body formation takes place during foetal life, when the body is hidden from observation. But of far greater importance is the fact that foetal nutrition is so independent of maternal nutrition that the infant in the womb is apparently shut off from most of the known causes of diseases. It is a parasite living on sterilised food, which it gets from the tissues of its host. The foetus is, therefore, with but few exceptions, not directly affected by those diseases which attack its mother, and though some toxins occasionally filter through into the juices of the foetus, yet the specific organisms of disease are rarely able to do so. This comparative immunity of the child before birth so cuts away the ground from theories which might otherwise have been advanced as to the causes of congenital malformations that we have little to consider

but some internal causes. And these internal causes are so much more subtle than those which give rise to post-natal diseases that they are, for all practical purposes, non-existent. But though, generally speaking, we have no evidence that congenital malformations are otherwise than spontaneous, it is possible to prove by direct experiment that they have causes. For example, Dr. Ballantyne,* alluding to the researches of Féré on the effect of various toxic substances in the production of monstrosities, says: "The results of Féré's experimental work were very striking. He found, for instance, that there was a direct relation between the teratogenic and the toxic power of poisons; this was well borne out in connection with the alcohols." Féré publishes a table of results tending to prove that those which were most toxic were also most teratogenetic. He showed, in fact, that there was a continuity in the results of intoxication, and that what was bad for the post-natal individual would produce arrest of development, local and general, in the foetus. But strange to say, contrary to what happens in after life, he did not find that any particular toxin produced teratological results in one organ more than in another. Dr. Ballantyne regards the work of Féré as of great importance, partly for its own sake, and partly because it helps to break down the dividing wall between ante-natal and post-natal pathology. The trend of these and of some other investigations is to prove that in the production of pre-natal deformities there is no radical difference between such toxins as alcohol and lead and the toxins of syphilis and tubercle, and that the same substances give rise to pre-natal as to post-natal developmental disorders, and in the same degree. More will be said on this subject further on (see p. 67). Another great difficulty which prevents our understanding the mode of production of the pre-natal malformations is the fact that many of them are handed down from parent to offspring, so that their causes must not only be very subtle but very remote. In short, the problem of the ætiology of most congenital deformities is so difficult and so involved that we acknowledge our inability to unravel the knot by cutting it. We declare that they have no cause, and are content with the bare assertion of their peculiar features. Observation has shown that they do not occur in epidemics, but sporadically, though there seems to be good reason for believing that they are more common in some districts than in others. In other words, they show a tendency to occur endemically. It has been observed that they are more common when the conditions of life are unhygienic or depressing.

* 'Manual of Antenatal Pathology and Hygiene,' vol. ii, p. 217.

Wild animals brought up in captivity are, apparently, more often malformed than when they live in their natural *habitat*. Pre-natal malformations, as has already been said, are also hereditary, for they are sometimes handed down from father to son, or occur amongst brothers and sisters, though, curiously enough, some forms are far more hereditary than others.

It must also be noted that different kinds may occur together, either in the same individual or in different members of the same family; and a malformation in one member of a family may be transformed into a malformation of a different kind in another member. No one would think of treating them medicinally, for they are looked upon as hopelessly incurable, save by mechanical methods only.

Tumours.

In regard to the tumours, however, there is ample scope for hypothesis, for there are innumerable influences around the post-natal human being, some of which may contain the explanation of their origin. Hence many hypotheses have been formulated to account for them, but in no case can these be regarded as satisfactory.

On inquiry into the characters of tumours, it is soon manifest that they can be divided into two great classes, namely, innocent tumours and cancers. The former consist of masses of cells of the same type as the tissues from which they spring. In other words they are indicative of a quantitative change. On the other hand, the cancers differ widely from the tissues or organs upon which they are situated, and signify a true qualitative change. As we have already seen, cancers are not really growths, but degenerations. The line of division between these two great classes is fairly abrupt. It is true that some innocent tumours are prone to degenerate into cancers, but nothing is better calculated to show that there is a radical difference between them than the striking alteration in the behaviour of a growth after it has become malignant. At the same time, a tumour necessarily implies the presence of some degeneration as well; and *vice versâ*, degeneration equally involves a certain amount of overgrowth. An innocent tumour is an excess of growth in the first place, the degeneration being a consecutive change, whereas the malignant tumour is primarily and essentially a degeneration, growth being merely one of its manifestations.

Innocent tumours.—However much they differ in form, there is close correspondence on the clinical side between those pre-natal

defects of growth which we term malformations and the post-natal excesses of growth which we term tumours. Thus the innocent tumours, like the malformations, are cryptogenous or *idiopathic*. They have a cause, but that cause is so hidden that for practical purposes it is non-existent. They also, like the malformations, occur not in epidemics, but in scattered instances—that is, *sporadically*—though they seem to be more common in some districts than in others—or, in other words, occasionally show *endemic* tendencies. They are *incurable*, except by mechanical means.

In addition, it may be noted that they are *progressive* in their course. This progress continues only up to a certain point and then stops, its duration often corresponding with the natural growth of the part upon which it is situated. Thus those tumours of cartilage and bone, which are known as osteomata, usually cease growing at puberty, when normal bone growth virtually stops. Fibromyomata of the uterus do not usually increase after the cessation of sexual life. It is true that some innocent tumours, if left alone, grow to such an enormous size as to convey the impression that they will continue indefinitely, but it is nevertheless true of innocent tumours as a whole that their growth is not indefinite, but tends spontaneously to come to an end.

Malignant tumours.—Just as innocent tumours show themselves to be true errors of growth by terminating at some period of their career, so the malignant tumours indicate that they are errors of development by continuing, like normal development, while life lasts. So true is this that if a myoma of the uterus, an adenoma, or any other innocent tumour, take on a fresh lease of growth after it has apparently ceased, we regard this as important evidence in favour of its having undergone transformation into a cancer. The carcinomata and sarcomata are not, like the innocent tumours, mere passive accumulations of piled-up cells, but are aggressive, actively invading other parts of the body from those in which they start. In this way they usurp the nutrition of the body, and by means of toxins or in some mysterious manner sap its vitality, causing the whole organism to become thin and exhausted, finally bringing about its destruction. They do not select those organs which are in most active use, but tend rather to appear where development is on the wane. They begin, as a rule, during the retrogressive stages of development. Tissues which are undergoing natural senile involution before the rest of the body becomes old, such as those of the uterus and breasts, are especially prone to cancer formation, and the same may be said of tissues which are undergoing fibrous, epithelial,

or other abnormal proliferation. The tongue in ichthyosis linguæ, the goitrous thyroid, the cirrhotic liver, warts and nævi, sebaceous adenomata, rectal adenomata, and other tumours of the declining periods of life, are all more prone to malignant degeneration than are healthy tissues.

Hence malignant degeneration resembles the innocent new growths in many respects, though it goes beyond them in others. It must, like the tumours, be regarded as essentially *idiopathic* in spite of the fact that its appearance may be fostered by certain general predisposing causes, or that it may be stimulated into activity by local irritation. Seeing that such causes as these are more abundant in some countries than in others, it follows that cancer must also be more common in certain parts than in others. In other words, though it occurs here and there, or *sporadically*, it seems, in some instances, to occur more or less *endemically*. It is also well known to be *incurable* by drugs, is on rare occasions *hereditary*, and is *progressive* in its course.

In regard to the foregoing characters the malignant degenerations keep company with the innocent new growths, but we now come to the parting of the ways. They are, as their name implies, not only progressive up to a certain point, but there is no end to their growth but death. They are *pernicious* and *malignant*, or *fatal*. Moreover, their progress towards an end is not entirely continuous, but is irregular, cyclical, or *intermittent*, for few sarcomata or carcinomata run their course without showing some signs of temporary acceleration or amendment.

Structurally the malignant tumours always display that form of degeneration which consists in a regression to a primitive type of cell. The organ which happens to be the seat of the disease continues its work unaffected until the encroachment of the cancer mechanically puts a stop to its function. Cancer is an integral process as regards the cell, but is a parasite or an external process in respect to the organ. In other words it is a *degeneration*, and a degeneration of the cell as distinguished from the organ.

III. Diseases of Mixed Intrinsic and Extrinsic Origin.

A number of scattered diseases still remain which cannot be included in either of the groups already described. They can neither be attributed to intrinsic influences alone, nor can they be said to be solely the result of external causes. Among the most important of these are the different forms of *leukæmia*, *splenomegaly*,

pernicious anæmia; the muscular dystrophies; the various scleroses of the brain and spinal cord; cirrhosis of the liver, and primary Bright's disease; rickets; obesity and emaciation; myxædema, cretinism and Graves's disease; the status lymphaticus; Addison's disease; simple gigantism; scleroderma and ichthyosis; osteitis deformans and osteomalacia. These disorders, like the tumours, may, as we have already seen, be divided into two classes—to wit: the defects or excesses of growth, and defects and prematurities of development (degenerations). But, unlike the tumours, they are, one and all, diseases, not of individual cells, but of collective cell groups, or organs.

Class I. The Primary Defects and Excesses of GROWTH or Organs.

Simple spontaneous undergrowth and overgrowth of organs have already been alluded to, and it is now only necessary to accentuate the relation they bear to the corresponding affections of cells or cell groups on the one hand, and to the errors of development of organs on the other. They consist in a quantitative change only, without any notable alteration in quality. In a word they are simple hypoplasias or hyperplasias. But, as with the tumours, a qualitative change does take place, though it is but a slight one, for all organs which are either abnormally small or abnormally big are more prone to undergo degeneration than are those of a natural size. In the same way that a papilloma or adenoma is more unreliable than normal tissue, and has a tendency to become cancerous, so also both the undergrown and the overgrown thyroid glands are more likely to degenerate and to become fibrous than is the gland of ordinary size. Hence that form of myxædema known as cretinism occasionally results from the fibrous breakdown of an unduly small thyroid, and adult myxædema sometimes sets in as a sequence of uniform overgrowth, such as we meet with in Graves's disease. Similarly, the brain of the demi-microcephalic imbecile and of the genius are both more likely to degenerate than is the brain of mediocre size (Dr. Langdon Brown). Primitive excessive growth of organs, like excessive growth of cells (innocent tumours), is not only *idiopathic*, but is sometimes hereditary, and, though sporadic as a rule, occasionally shows endemic tendencies. It resembles the tumour process also in that its course is *progressive* up to a certain point and then stops. That which occurs in variable organs, such as the thymus or thyroid gland, shows *interruptions* or changes in its course like those which take place in normal growth, and under these cir-

cumstances it is possible for the improvement to go on to such a degree that the disease entirely disappears. No drug seems to have any influence in terminating its career, so that in this respect it is *incurable*. Being a growth it is prone to appear at times when normal growth is most vigorous, and to affect to the greatest degree those organs which are normally most fluctuating in their growth.

Having made these bare statements of some incidents in the structure and behaviour of undergrowth and overgrowth of organs, let us now proceed to deal with similar disorders of development. In the above list these are printed in italics, whereas the disorders of growth are in ordinary type.

Class II. The Primary Defects of DEVELOPMENT and Pre-maturities of Organs.

Most, if not all, of the maladies which are now alluded to seem to owe their appearance partly to the action of some external irritant. Thus, osteitis deformans may begin apparently as the result of a kick, granular kidney may be due to gout, and cirrhosis of the liver to alcohol. Similarly splenic leukaemia may seemingly be induced by malaria, while pernicious anaemia may, according to Dr. Hunter, have its origin in intestinal toxins. But after saying all that can be said in favour of the origin of these diseases from such causes, one is compelled to admit that as causes they are very inadequate. Take, for example, atrophic cirrhosis of the liver. In no disease is it more evident some outside agent is at work, acting so as directly to produce a morbid condition. Yet we know that alcohol may be taken in the most inordinate excess during most of the years of a man's life without producing even a trace of disease, though in another man a quite temperate use of wine or beer will result in cirrhosis of most pronounced type. Yet another individual dies from cirrhosis though he has never tasted alcohol in any form; and, what is perhaps most emphatic of all, cirrhosis of the liver is sometimes met with in the lower animals, though they have been fed on a diet in which alcohol has no existence. Cirrhosis of the liver may, therefore, be regarded as having two origins: it is, in the first place, idiopathic, having no discoverable first cause; and in the second it owes its appearance to the action of the toxin, alcohol. From these facts we can only suppose that some individuals are born with the tendency to cirrhosis of the liver, and that this tendency may never assert itself as actual disease;

that in others the stimulus of the daily use of alcohol may be sufficient to upset the equilibrium of health; or, lastly, that the equilibrium may be so easily upset that we can find neither alcohol nor any other cause to account for the appearance of the cirrhosis, so that for the sake of convenience it is termed idiopathic.

We may speak in a similar, and perhaps still more forcible, manner of other members of the group. Some of these, as, for example, osteomalacia, local gigantism of the extremities, and pseudo-hypertrophy of the brain, make their appearance so mysteriously that we confess our complete ignorance of their causation, and at once dub them idiopathic. In short, of not one member of the group can we say that we know its true cause. Whenever one of these diseases appears it has already had a potential existence quite apart from the excitement which determines its actual outbreak. It is like some substance existing in saturated solution, which takes on a tangible form only when a foreign body is thrust into it, or when it is agitated by some external shock. But often we can detect no disturbance of any kind, the crystallisation being apparently spontaneous. This feature brings the group into close relation with the congenital malformations, new growths, and cancers, whose real origin is equally beyond our comprehension. Thus we know that cancers may be excited into existence by prolonged irritation; but though the chimney-sweep's cancer is evidently due to soot, the smoker's cancer to his pipe, and cancer of the breast and uterus to child-bearing, this does not prevent us from going into laborious and costly investigations as to their true origin. Though we acknowledge the presence of certain superficial causes, yet we regard these disorders as essentially idiopathic.

Hence we arrive at the conclusion that toxins and other irritants, though they may be of great importance, are only contributory causes of the diseases of this third group, and that in regard to their primary, or essential, causes, we can only confess our ignorance. This is equivalent to saying that, of the three classes into which diseases may be divided, this group approaches far more closely to the second class than to the first. In other words, the diseases of the group are, like pre-natal malformations and tumours, of intrinsic origin, rather than extrinsic, like the infectious fevers. This view is fully borne out by further inquiry, for we shall find that the disorders of the group follow the same clinical outlines and are constructed on the same plan as some of the disorders of the second group. Their whole course and character show that they proceed in the first place from within.

Though the remote causes of these maladies are beyond our ken, the proximal causes are recognised. It is true they are often very problematical in any given case, yet we are fairly sure of them as a whole. Now these causes are of such a kind as to throw a strong light on the nature of the disease to which they give birth. They seem to be all of a depressing nature, and are of the same class as those which are generally suspected of favouring the appearance of the pre-natal malformations and of cancers. The depressing emotions, such as shock, grief, disappointment, failure in business, gloomy or insanitary surroundings, and dispiriting influences of a similar nature are all mentioned in text-books as causes of different members of the group.

VII

THE CAUSES OF DEGENERATION

Among these are the toxins, especially that of *syphilis*, and *alcohol*, and *lead*. The effect of all three is to deteriorate, both function and structure being reduced from a higher level to a lower. Though each acts in its own special way, selecting certain tissues in preference to others, the ultimate result is similar. Each reciprocates or accentuates the action of the other. Degeneration is also set up or revealed by certain physiological or para-physiological causes, such as pregnancy, heredity, locality, race, and habit. *Pregnancy* is an important factor in the production of leukæmia, pernicious anæmia, Addison's disease, osteomalacia, rheumatoid arthritis, Bright's disease, and acute yellow atrophy. *Heredity* accounts for the transmission either of the same disease or of disease of the same kind (transforming heredity). *Locality*, *race*, and popular *habit* tend to introduce an endemic element. When causes can be traced for the pre-natal defects of development, they are found to be of the same nature as those which cause the post-natal degenerations. Among the chief are *syphilis*, *alcohol*, and *lead*.

ALLUSION has just been made to the influence of toxins in producing premature senile degeneration. So important are these toxins that it is advisable to enter into the subject with more detail, referring especially to the three chief toxins, namely the syphilitic, alcohol, and lead. Other causes of degeneration will then be dealt with, particularly those produced by pregnancy, heredity, locality, and habit.

The Toxins.

Recent laboratory research has greatly helped to bring home to us the importance of the bacterial toxins in originating or hastening the processes of degeneration. All the toxins have this property in greater or less degree, no matter by what name they are called. Among these toxins three may be selected as examples, partly because of their importance, and partly because they serve to illustrate the essential similarity of the action of these agents, from whatever sources they may be derived. One of these is the poison produced by an animal parasite, the *Spirochæta pallida* of syphilis ;

the second comes from the saprophytic vegetable parasite *Cerevisæ fermentum*, or yeast; and the third is the mineral toxin, lead.

In all intoxications it is necessary to distinguish between the immediate and the remote effects. The immediate effect, for example, of syphilis, alcohol and lead is irritative. They break in upon the normal harmony of the cells and organs with the disturbing effect of an invasion. The incidents and details of this invasion differ with the nature of the invader. In syphilis the organism which produces the toxin has itself become lodged in the body, and is able to pour out its toxin continuously, producing the syphilitic fever, sore throat, skin rashes and other indications of disorder. Lead is a toxin which gains access in repeated doses from some external source and is at first stored in the body, accumulating until a point is at last reached beyond which the toleration of the body can no further go. Colic, anæmia, cachexia, and other symptoms then mark the sudden onset of a grim struggle for predominance on the part of the defensive forces of the body against the invader. Alcohol is similar to lead in its mode of action, but is not cumulative and excites far more resistance at the outset, so that the initial symptoms of intoxication are greater and are diffused over a wider area.

These are the immediate effects. The remote effects are comparable with the deterioration of a nation which sets in as the result of prolonged or repeated invasions by hordes of barbarians. These also differ with different lesions and to a similar degree.

(1) **Syphilis** is so important a factor in producing degeneration that hardly a disease of the developmental group is not either produced or simulated by it. Syphilis, once it has gained access to the body, is like degeneration itself, ubiquitous; and, at the same time, acts so insidiously, and comes into such intimate relationship with the minute structure of whatever organ it affects, that it interferes with development at its very roots. Acquired syphilis of the tertiary form gives rise to collections of round embryonic cells (gunmata), reminiscent of the embryonic cells which constitute such a feature of the senile organ, and occur so abundantly in the primary degenerations of the liver, kidneys and other organs. These round cells also turn into fibrous tissue, and form tough contracting bands, after the manner of the round cells of old age. It is true that as a rule the new syphilitic tissue is far more scattered or disseminated, coarse and irregular in its distribution than that due to senile change, but these are secondary details, and are not

of fundamental importance. Certain primary diseases of the nervous system and of other organs are also disseminated in a similar way, and in exceptional cases, syphilis may produce widespread uniform fibrous degeneration of organs closely simulating that produced by natural old age. Further, it may give rise to arterial sclerosis, cirrhosis of the liver, and sclerosis of nerve-tracts and other parts, hardly to be distinguished from the corresponding non-syphilitic fibroses. Moreover, the disease in a still more remote form may produce results (parasymphilitic) which cannot be distinguished from ordinary infantilism, "idiopathic" malformations, or degenerations. Tabes and general paralysis seem to be the chief para-symphilitic affections of acquired syphilis, and the changes they produce are identical in character with those seen in the idiopathic nerve degenerations. In so-called hereditary syphilis there is one more similarity to account for, and that is the fact of transmission. This, and the fact that the "hereditary" form even more closely resembles non-symphilitic degeneration, and may give rise to granular kidney, to cirrhosis of the liver, arterial sclerosis or other fibroses, to infantilism, and to congenital malformations, which are exactly like the corresponding idiopathic disorders, brings syphilis even more nearly into line with the degenerations of spontaneous appearance. In short we may say of syphilis that it is a disease which has its origin in acts of vicious generation and most fittingly manifests itself in vicious degeneration.

(2) **Lead** is less sensational and more uniform in its effects, acting often so quietly and insidiously that its influence is apt to be overlooked. It gives rise to the more generalised scleroses of the nervous system and the kidneys, and probably, but less often, of other organs.

(3) **Alcohol** has already been referred to as the toxin of the yeast microphyte. It is a stimulant-narcotic. Its narcotic action has been fully proved by observations on animal and vegetable cells, on the sense organs, on the processes of digestion, and on the mental faculties. The experiments of Kraepelin, Parkes, Ridge, Metchnikoff, Richardson, and others demonstrate that not only large, but also small, doses of alcohol are narcotic or inhibitory. But the governing mechanism of the human body is of such a nature that a widespread inhibition of function may show itself quite as much in exhilaration as in depression. Indeed, the indirect exhilaration may be far more obvious than the direct narcotism. Hence, a man may be so affected with paresis of co-ordination as to be manifestly unable to control the movements of his muscles, and yet at the same time may enjoy such a flow of good spirits, accompanied with a feeling

of well-being so pronounced, that he is not only not obviously depressed, but is, in vulgar parlance, said to be "elevated." This apparent contradiction is to be accounted for by the fact that the chief regulating principle of the body consists in the friendly opposition of antagonistic forces. For example, the accelerators of the heart are balanced or held in check by the inhibitors, and the constrictors and dilators of the arteries maintain a fluctuating equilibrium of a similar nature. In such cases it is obvious that the depression of one side of the balance is equivalent to the corresponding elevation of the other. And this is apparently how alcohol operates. It does not exert a depressing effect on both sides alike, but is selective, after the manner of a tissue stain. It quickens the action of the heart by depressing the action of the vagus; lowers arterial tension and increases the blood supply by depressing the vaso-constrictors; and in a similar way interferes with the mental and moral balance by producing a paresis of judgment and self-control. Hence, the stimulant effect of alcohol is the direct outcome of its narcotic action. Our higher qualities are, generally speaking, those which are last acquired, and our baser qualities are also *basic*. Alcohol tends always to strip off the surface layers of better sort, and to lay bare the more primitive bed-rock of character. This progressive mental degradation of the toper, in which the higher and more recent qualities succumb sooner than the older and lower, is well expressed in the line "to be now a sensible man, by and by a fool, and presently a beast."

Such a disturbance of bodily function of necessity has its corresponding structural changes. Each of the twin actions of alcohol is both the cause and the occasion of material alterations, and each is detrimental to the human machine.

In the first place, the narcotic action is inimical to its resisting power to attacks of micro-organisms. The tissues of the alcohol drinker are more vulnerable than those of the water drinker. According to Metchnikoff alcohol diminishes the phagocytic properties of cells, and the experiments of Delearde, and, more recently, of Professor Laitenen, show that immunity in general is seriously impaired by even moderate doses of alcohol.

In the second place, the stimulating effect is injurious. It is to a large extent the result of an increased flow of blood. Were this increased blood supply occasioned by natural causes no harm would follow, for it would then be furnished only in such quantity as would correspond with the demand. But the flow of blood to the stomach, skin, and brain of the alcohol drinker is founded on no such

physiological reasons. It is due to a temporary insanity of the circulatory apparatus and is purely artificial. Hence, any increase of gastric juice, any extra warmth of the skin or exaltation of mind so produced is pathological, for it is due to a morbid congestion and not to a natural flush. The action of alcohol upon the healthy stomach is essentially that of a disorder, and carries with it all the evil which the word implies.

In addition to these two actions there is another effect of alcohol which in some degree mitigates its toxic properties. This is the so-called food-action. It is recognised that when alcohol is taken in moderation—say an ounce and a half (40 cm.) a day—it is decomposed, and furnishes the body with a corresponding amount of energy. But there is no reason to suppose that during the time that this decomposition is in progress the narcotic action is in abeyance. On the contrary, it has been proved up to the hilt that these decomposable quantities are also narcotic. Moreover, alcohol does not seem to possess any advantages over other forms of food. Alcohol as a food is comparable with castor-oil, which is also a combination of drug and food, or with a mixture of small quantities of opium with large quantities of milk. The chief distinguishing feature of a food as compared with a drug is that, whereas the drug is partial in its action, selecting one part in preference to others, food is strictly impartial, supplying each cell, tissue, organ, in exact accordance with its physiological necessities. Alcohol cannot be regarded as a normal food or drink, for it is taken independently of hunger or thirst, requires no digestion, is selective in its action, and a disturber of function. In reality it is a drug which imitates a food.

It is impossible to estimate with any approach to accuracy the damage done by alcohol when taken in such strictly moderate quantities as to produce no obvious effect on the blood-vessels, while no undecomposed residue escapes from the kidneys. The statistics of insurance societies seem to show that even under such circumstances there is some deleterious result. Mr. Moore, the actuary, in summing up the sixty years' experience of the "United Kingdom Temperance and General Provident Institution," dealing with just 31,000 life policies, states that if the figures be analysed after all modifying factors have been taken into consideration, "the abstainers show a marked superiority to the non-abstainers throughout the entire working years of life, for every class of policy and for both sexes, however tested." Moreover, he goes on to say, "the non-abstainers assured in the Institution are good average lives, generally

equal to the best accepted standard of assured lives.” In his comment on this paper the editor of the ‘British Medical Journal’* points out that the experience of the abstainers’ section is from 26 per cent. to 45 per cent. superior to that of the moderate drinkers’ section “in the active-working, valuable years of life,” *i. e.* between the ages of twenty-five and sixty-five. He concludes that “a careful study of the statistics fails to reveal any other circumstances of life, except abstinence from alcoholic drinks, which is a likely cause of the remarkable superiority in life prospects shown by abstainers. It must be frankly admitted that steady, persistent abstinence from alcohol is, in the light of the experience, an important factor in securing healthy and long life.” These statistics are often passed over as of no value by those who have already come to contrary conclusions. This attitude is, however, unreasonable, for actuaries not specially interested in the figures say that they bear investigation. They have been carefully collected, have the advantage of approaching the subject from a cold financial aspect, not from the biased view of the propagandist, are remarkably consistent, and, moreover, tally with all that is known of the pathological action of alcohol upon the body. They represent precise, formal facts, and as such compare favourably with the indefinite, inaccurate impressions and appeals to custom, to national comparisons, to appetite, and to social usage which are urged by those who deny their value. The alcohol question is one of immense importance and complexity, and few can afford the time, or are furnished with the necessary scientific equipment, for appreciating the value of the evidence for and against. But we must all agree that ultimately these scattered facts may be made to converge by means of statistics and brought to a focus.

To find the effect on the death-rate is the only possible way of arriving at a conclusion. It is as safe a criterion of the good or evil of any widespread social custom as are the quotations of the stock exchange a safe criterion of the influence of great political changes.

It is unreasonable, or even absurd, to regard, as some do, the grosser results of alcoholism, such as cirrhosis of the liver, delirium tremens, alcoholic insanity, or the prevalence of drunkenness, as the sole indications of its debasing properties. All the careful work that has been done on the subject goes to show that the less sensational effects wrought by the habitual drinking of small quantities are, in the mass, of far greater consequence than those produced by so-called excess. The deteriorating and lethal effects occur to a

* ‘Brit. Med. Journ.,’ 1904, vol. i, p. 156.

degree which corresponds with the amount swallowed. Hence many deaths now attributed solely to pneumonia, to bronchitis, or other common disease, ought, in reality to be attributed to the sapping of vitality by many previous years of the daily temperate use of wine and beer. Evidently a drug which slowly breaks down the protective mechanism of the body, without producing any very noticeable effect, is capable of doing an immense amount of mischief, too insidious to be estimated directly. The only possible way of arriving at a legitimate conclusion is by comparing the death-rate of drinkers with that of non-drinkers.

The results of researches on the functional consequences of alcohol are in every respect in keeping with all that is known of its structural effects.

Nothing seems better calculated to give rise to that mixture of deterioration with overgrowth, which is characteristic of degeneration. Alcohol stimulates growth while it hinders development. Under its influence numbers of new cells of a low order of development are prone to make their appearance in the alcoholised organs, to replace those of higher type. The result of this growth is seen in the fibrosis of organs; and alcoholic fibrosis, like syphilitic fibrosis, may exactly resemble the fibrosis of old age and of certain degenerative diseases.

In fine, there is no fundamental difference between the degenerative effects of alcohol and of syphilis, though the former is more mild and widespread, and the latter more localised and malignant.

It may be objected that too much attention is given to the subject of alcohol as a proximal cause of the disorders of growth and development. But, when we know that more than half of them may be stimulated into existence by alcohol; and that it is in some cases the chief element in their production, we are justified in insisting upon the significance of this drug. It seems to be agreed that such conditions as cirrhosis of the liver, primary Bright's disease, and that important class of diseases for which the term "insanity"* has been exclusively employed, owe their existence, to a large extent, to alcohol. Hence, alcohol must occupy a conspicuous place in the study of degeneration. It seems to rule over such processes like a presiding daemon. In the words of Dr. Dickinson, it "helps time to produce the effects of age; and, in a word, is the genius of degeneration."†

* "Twenty per cent. of the admissions to the London County Council Asylums were due to drink." Dr. Mott, 'Lancet,' 1905, vol. i, p. 862.

† 'Med.-Chir. Trans.,' 1873, vol. lvi, p. 59.

Syphilis, alcohol, lead are in one respect like the pigments used in staining tissues; each picks out some organs in preference to others. One leaves its mark on the liver, another on the nervous system, and so on. But they overlap to a much greater extent than do the pigments, with the result that when two of these toxins work together the one reinforces the other. For example, lead gives rise to granular kidneys, and so does alcohol, but the kidneys are never so likely to become granular as when both these agents are in action at the same time. And this accentuation may ensue either as the direct consequence of the alcohol itself, or indirectly by means of the gout which the alcohol sets up. So also it is well known that the effects of the syphilitic poison are greatly enhanced by alcoholism. When alcohol and syphilis work together the alcohol does not always give rise to its favourite disorders, such as cirrhosis of the liver or kidneys, but may light up certain parasymphilitic diseases, such as general paralysis or tabes. It may even be the cause of an outbreak of gummata. Furthermore, each of these three is far more efficient as a disease-producer when it acts in conjunction with any of those depressing circumstances which we have referred to as less tangible causes of the degenerative diseases. A plumber may be physiologically saturated with lead and show no signs of disease, but let him indulge in an excess of alcohol, and he immediately has colic, or in a short time begins to suffer from chronic Bright's disease. A similar result ensues if, instead of drinking inordinately, he be thrown out of work, be convicted of some crime, bereaved of one of his children, or endure the shock of a serious accident. So is it also with syphilis and alcohol. Each is more effective as a disease-producer if it act in conjunction with poverty, anxiety, or depression of any kind.

Reciprocity between alcoholism and degeneration.—Nothing shows more clearly the close relation of alcoholism to degeneration than the way in which these two act and react one upon the other. If alcohol produce degeneration, so also does degeneration facilitate, or even induce, alcoholism. In some cases of insanity or crime occurring in the victims of alcoholic indulgence it is impossible to say whether the mental or moral obliquity is the consequence of alcohol or is its cause, or is both cause and consequence; and if both, which is the more important of the two.

One of the chief distinguishing characters of the diseases of retrogressive development is intermittence, and this also is often a conspicuous character is alcoholism. Many alcohol inebriates have no difficulty in reducing their consumption of stimulants to the

limits of moderation for weeks and months together, but every now and again, at uncertain intervals, and often for no reason whatever, the desire to drink seizes hold upon them with such overwhelming intensity that they give way, and for a few days yield themselves to all the allurements of a debauch. In short their lives consist of a cycle of moderation or abstinence, succeeded by a short orgy of excess, and, following that, a still shorter period of remorse and depression. Sometimes the excitement of the drinking fit leads on to the insanity of delirium tremens; or the depression which sets in after the drinking bout ends in profound melancholy and suicide. In this way acute alcoholism shows its connection with the degenerations of the nervous system, especially with the alternating forms of insanity.

This interchanging relation of alcoholism with nervous instability and degeneration can only be fully understood when we observe how intimate are the relations of alcohol with physiological cycles. Thus it has been noticed that periodic drinking in women is often coincident with the menstrual periods, and it is well known that many women drunkards attribute their intemperance to drinking habits which have started with tipples of gin or other spirit taken to relieve the pains of dysmenorrhœa.

Yet that alcohol alone is unable to bring about degeneration is suggested by the way in which it selects those who are known to have an hereditary tendency to premature degeneration. Such a vulnerability is, perhaps, shown most conspicuously in the records of lunatic asylums, and is illustrated with great force by Dr. Mott. When opening a discussion on the relations of heredity to disease,* he said that "a quantity of alcohol which is insufficient to affect a stock with a stable nervous system acts with peculiar force upon the nervous system of the mentally unstable, rendering him anti-social, and bringing him into a hospital, workhouse, lunatic asylum, or prison. Thus in all my extensive experience at the London county asylums, where 20 per cent. of the inmates are said to be there on account of drink, I have only once seen a case of cirrhosis of the liver with ascites, and that was a notorious police-court character, Jane Cakebread, who was convicted nearly 400 times before she could be certified as incapable of taking care of herself. Yet I have, during the past six months in my hospital practice, had several cases of alcoholic cirrhosis with ascites from long-persistent spirit drinking, without mental symptoms; and Haycraft states that drink may be looked upon as a selective agency constantly thinning the ranks of those who are weak enough by

* 'Brit. Med. Journ.,' 1905, vol. ii, p. 1087.

nature to give way to it, and leaving unharmed those with healthy tastes and sound moral constitution."

This leads us to one aspect of alcoholic indulgence which cannot be passed over, especially as it acts to some degree in mitigation of its evil effects. If alcohol facilitate the descent of the drinker, how can any man who drinks his daily glass of wine or beer escape deterioration? Yet it would be absurd to assert that the ordinary daily use of wine or beer inevitably leads to such consequences. On the contrary, there is an impression prevalent that it is a sign of strength of character to be able to drink to excess without being inebriated. Our forefathers showed the highest respect and admiration for the man who could drink his two bottles of port without losing self-control, and regarded the man who could not drink without being immediately fuddled as a milksop and possessed of no strength of character. There can be no doubt that this belief is still prevalent, though to a less extent, and that it accounts for much of the drinking of the present day, as well as for much of the contempt that is even yet dealt out to those who abstain. As a matter of fact, as is the case with so many instances of widespread, deeply rooted beliefs, this conviction is founded upon a basis of truth. We have just seen that the drinking of alcoholic liquors does more damage to those who are already the subjects of plumbism and syphilis than it does to those who are sound. So also is it with those who are debilitated from other causes. Hence, to the well-to-do man of education and refinement, whose life has proceeded from success to success, his customary wine holds out no inducement to debauchery, and its bad effects are of the slightest; whereas to the out-at-elbows street loafer, unemployed, depressed with cold and hunger, and with a heritage of all sorts of degenerating mental and bodily disabilities, the power of the public-house for evil is only limited by his poverty. Alcohol, in brief, acts at the best advantage when associated with other causes of degeneracy. But just in the same way that adversity strengthens the strong, so to the healthy man of strong character and with only the ordinary tendencies to vice the adversity into which his tissues are plunged by his daily small libations of alcohol may possibly tend rather to strengthen than to weaken him. In short, the same process is constantly going on in the ordinary wine drinker as that which is produced by the injection of toxins when we wish to confer immunity. Indeed, there is hardly room for doubt that the use of alcoholic liquors in gradually increasing doses eventuates in increased immunity to the poison. No fact speaks stronger than this that alcohol is a toxin,

for we know of no agent save a toxin which can have such an effect. At the same time it must be insisted upon that the immunity conferred by alcohol is only good against itself and others of its class of stimulant-narcotics. We have seen that, according to Metchnikoff, alcohol diminishes the phagocytic properties of phagocytes, and common experience bears emphatic testimony to the increased susceptibility of the alcohol drinkers to bronchitis, pneumonia, and other microbial infections.*

Other Causes of Degeneration.

In addition to the syphilitic, alcoholic, plumbic, and other toxins, certain *physiological influences* have a very decided bearing on the production of premature senility. The chief of these are *pregnancy* and *heredity*, and the less definite circumstances of *locality*, *race*, and *habit*.

Pregnancy.—The effect of pregnancy in giving rise to, or revealing, certain diseases of the third group need not now be gone into at length, because fuller reference will have to be made to it when we come to discuss individual diseases. But at this point it is necessary to realise that pregnancy and the puerperal state are no more than physiological epochs, events of exactly the same nature as those “changes” which mark off the seven periods of life and are most pronounced at birth, puberty, and the menopause. Of the two pregnancy is by far the more potent. It seems, indeed, to be of more effect than the ordinary changes of life, probably in part because it is more erratic in its appearance, and partly because its changes are concentrated within the compass of a few months. But the chief reason is, no doubt, that during pregnancy all the efforts of the body are put forth in the work of development. Hence, while leukæmia, pernicious anæmia, myxœdema, Addison’s disease, osteomalacia, rheumatoid arthritis, and, to a less extent, some other diseases, are prone to arise during one of the ordinary climacterics, they are still more likely to occur as the result of pregnancy and the puerperal state. We have seen that certain organs are always sympathetically affected by normal pregnancy, and some much more than others, just those organs which are most susceptible to physiological changes being also those which are most often diseased. Thus some of the bones, and particularly the pelvic bones, undergo alterations to a far greater degree than do other bones during

* See Sir Victor Horsley and Mary Sturge, ‘Alcohol and the Human Body,’ ed. ii, p. 18.

pregnancy, and these same bones are also peculiarly liable to be affected first in osteomalacia. The blood undergoes changes in pregnancy in the direction of lymphocytosis, and therefore the disease leukæmia is prone to set in during this epoch. Pigmentation of the skin and alterations in the character of the urine, of the pulse, and of the muscular strength, sometimes so noticeable during child-bearing, are highly suggestive of some strain on the functions of the liver, the kidneys, and the supra-renal bodies, and apparently provide the physiological basis for the well-known occurrence of acute yellow atrophy of the liver, of Addison's disease, and of chronic Bright's disease in association with child-bearing.

Heredity.—The influence of heredity is shown in many of the diseases under consideration, and with increasing knowledge diseases are now regarded as hereditary which a few years ago were looked upon as incapable of transmission. Just in the same way that some forms of pre-natal malformation, some innocent tumours, and, possibly, some cancers are more often handed down by heredity than are others, so it is with the degenerations of organs. Some are often hereditary, others seldom, and a few never. Further, it has been pointed out that when malignant degeneration of cells is hereditary the disease tends to occur much earlier in life than when there is no such transmission. The same may be said of the degenerations of organs, for, in their case too, heredity is prone to go with an early age of occurrence. As a rule the form which the heredity assumes is of the kind termed "family" or "familial"; that is to say, the disease appears among brothers and sisters, not in parents and children. Hence we find that among diseases which show this proclivity there are, as a rule, distinct varieties distinguished by beginning at an early time of life, and it is these varieties in particular which are hereditary. Thus we recognise early forms of osteomalacia, of osteitis deformans, of arthritis deformans, of muscular atrophy, of myxœdema and of splenomegaly, and all of these early forms are far more likely to be transmitted than are the later or ordinary forms of these respective diseases. At the same time it must be observed that this tendency to be handed down may also be present in the later cases, though, as a rule, to a far less degree.

Another form of heredity which it is very important to recognise is indirect or *transforming heredity*, which consists in the transmission of a proclivity, not to the same disease, but to other disease of a similar nature. This form of heredity has already been alluded to as occurring in pre-natal malformations and in innocent and malignant

tumours. It is also found in the degenerations of organs, and is, of course, never convincing unless the association is very frequent and can be cleared from the suspicion of having a common outside cause, or unless the diseases are so rare that it is practically impossible for them to be associated fortuitously. Good instances of each of these two proofs are given by Kiernan and by Clifford Allbutt respectively. In that recorded by Dr. Kiernan* chronic Bright's disease, locomotor ataxia, club-foot, cleft palate, imbecility, deaf-mutism, Graves's disease, sarcoma, carcinoma, asymmetry, hermaphroditism, and various other stigmata of degeneration occurred in different individuals of the same family in the course of three generations. This extraordinary conglomeration of disorders of growth and development was apparently in great part due to inter-marriage, and to marriage with deformed or otherwise unsound outsiders.

The second instance is furnished by Professor Sir Clifford Allbutt † who has stated that he was "once called in consultation to a father and three children whose maladies were as follows: carcinoma, lymphadenoma, pernicious anæmia, and pseudo-hypertrophic palsy." Such a conjunction of three rare diseases cannot have been due to mere chance; their association in the same family, and their evident transmutation one into the other, in different individuals, is almost as good evidence of the heredity of each of them as if the same disease had occurred in all four members of the family.

The occurrence of degeneration in more than one organ of the same individual and its meaning.—We have just referred to the association of different forms of senilism in different members of the same family, and have recognised how important this fact is as testimony to the close relationship of these diseases. It is now time to refer to the occasional occurrence of different cryptogenetic diseases in different organs of the same individual. It is not infrequently noticed that an anomaly of pre-natal development, such as hare-lip, is accompanied by some other developmental defect, such as coloboma of the iris, or spina bifida. Occasionally several occur together. For example, in a case recorded by Dr. Corby‡ a youth of fifteen was found to be a true hermaphrodite; one leg was shorter than the other, he was knock-kneed, had six toes on each foot, and six fingers on each hand, was of feeble intelligence, and presented other indications of defective development of the thyroid gland. The cause of

* 'Medicine,' September, 1897, quoted by Talbot; 'Degeneracy,' p. 73.

† "Address to British Medical Association," 'Brit. Med. Journ.,' 1888, vol. ii, p. 237.

‡ 'Brit. Med. Journ.,' 1905, vol. ii, p. 710.

this condition could not be ascertained, but there was some hereditary influence at work, for another child in the same family was also an hermaphrodite. Clearly these pre-natal abnormalities are not grouped together in this way by mere chance; there must be some bond of correlation between them, so that certain organs are prone to be affected together.

But we see a similar association of diseases of post-natal growth or development, and in their case, too, a similar correlation is exhibited. Thus fibrosis of the liver is often accompanied by fibrosis of the kidneys, these organs having close physiological affinities. Arterial fibrosis usually goes with fibrosis of the kidneys; combined spinal cord degenerations with pernicious anæmia, or with osteomalacia. Sarcomata or carcinomata are often found in the subjects of osteitis deformans; chronic spontaneous splenomegaly is associated with fibrous degenerations of the liver; and there are many more associations of a similar nature to which reference will afterwards be made.

Effect of locality, race, habit, migration.—Though we see everywhere a tendency for the diseases of this mixed group to occur more in some districts than in others, yet this is far less a feature of the endogenetic diseases than of the ectogenetic. Indeed, we may say that while many of the latter, for example, the infectious fevers, leprosy, influenza, plague, are essentially endemic or epidemic, and all of them distinctly favour one locality over another, the endogenetic do so only in a minor degree. With the one class it is an essential feature, with the other it is only occasional and non-essential. In endogenetic cases it is due to some geographical peculiarity, such as that of deep, sombre valleys, or to the use of water laden with undeposited mineral *débris*, which is supposed to give rise to goitre. Some similar geographical circumstance seems to account for the more frequent occurrence of pernicious anæmia and of osteomalacia in some parts of Europe than in others; and perhaps for the prevalence of Addison's disease in Europe compared with its far greater scarcity in America. But it is impossible to say in some instances how much is due to soil, how much to race, and how much to habits of life or to other circumstances. In other cases the causes of the endemic element are pretty obvious. Thus it is fairly certain that the frequent occurrence of chronic Bright's disease and of cirrhosis of the liver in any district is largely due to the nature and quantity of the drinks in common use.

Sometimes a local disease area will be caused by the migration of the more healthy inhabitants, an example of which has been given

by Dr. Morrison, of Hereford,* who has pointed out that the county of Hereford has a larger proportion of the congenitally insane than any other county in England and Wales, and puts it down to the continuous emigration of large numbers of the best-developed of the population. This has led to greater relative deterioration of those left behind, and shows itself by increase in alcoholic excess, crime, goitre, insanity, tuberculosis, and, above all, in congenital idiocy and imbecility.

A similar process of migration of the fit, so as to leave a sediment of the unfit, has been in progress in Ireland for many years, and has brought about a similar tendency in the concentration of deformity, disease, insanity, and crime into one geographical area.

The Relations between the Causes of Pre-natal and of Post-natal Developmental Errors.

An inquiry into this subject shows that there is a close correspondence between the causes of those faults of development which occur before birth, and of those which constitute pre-senility and senilism. Thus among the chief causes of ante-natal malformations and defects of development are improper or inadequate food, misery, unsuitable surroundings, and other factors which are known to be of a depressing or inhibitory influence upon vitality. And just this same kind of circumstances is responsible for premature old age.

It may be objected that some of these causes are too indefinite to be of very much value as evidence, but this cannot be said of certain disease agents or toxins whose action is definite enough, and is capable of being followed, not only in the human being, but still more precisely in the lower animals. Ballantyne, in his work on 'Ante-natal Pathology,' shows that there are certain diseases in the parents which bring about debility in the foetus without actually infecting it, and that they may, in this way, be the cause of malformations or of defects of development. Thus the offspring of mothers suffering from enteric fever, tubercle, and septicæmia are in his opinion, and in that of other authorities, far more likely to be deformed at birth than are the children of healthy mothers, though in these instances it is of importance to note that the child may have neither enteric fever, nor tubercle, nor septicæmia. Again, certain diseases and disease-agents, or drugs, have been proved sometimes to pass directly into the tissues of the foetus, in spite of the filtering action of the placenta. These are mercury, phosphorus,

* 'Brit. Med. Journ.,' 1905, vol. ii, p. 945.

arsenic, copper, carbon monoxide and dioxide, tuberculosis, chloroform, ether, morphia, lead, syphilis, and alcohol. Now, it is significant that in regard to many of these there is no evidence that they do structural harm to the fœtus. This may be said, for example, of opium, ether, chloroform, carbonic oxide and dioxide, arsenic, copper; while others, such as mercury and tobacco, produce a certain amount of debility; and phosphorus, moreover, gives rise to lesions in the fœtus similar to those which it brings about in the mother. But with the last three on the list, namely lead, syphilis and alcohol, it is different, for they produce evil effects both upon the fœtus *in utero*, and upon the child after birth. And this fact is of extreme importance, for it appears that the effects wrought by these three consist, not only of debility, but also of definite pre-natal errors of development, and furthermore, these are just the three substances which we have already seen to be guilty of producing *post-natal* errors of development.

Of the trio, *lead*, according to Rennert,* is peculiarly apt to give rise to cranial anomalies, and especially to microcephaly. And Ballantyne goes on to say that "in Rennert's cases, the influence of syphilis and alcohol was apparently excluded. The localisation of the effects of the lead upon the brain and cranium is interesting when taken in conjunction with Porak's experimental results, in which the metal was found especially in the nervous centres." But this is particularly of importance to us, because lead also selects the nervous system of adults, and according to Dr. Fagget† produces atrophy of the brain, the other causes of this atrophy being senility and alcoholism. According to the same writer‡ it also produces a form of paralysis which is indistinguishable from progressive muscular atrophy, and, in truth, may be progressive muscular atrophy itself. Other visceral changes present in the lead-poisoned fœtus are irritative lesions of the liver and kidneys, including an arrest of development of the glomerular zone of the latter organs. This action on the kidneys to some extent coincides with the known action of lead in causing Bright's disease, though the part of the kidney most affected is not the same in both cases.

Syphilis, according to Fournier, has two sorts of hereditary consequences. It may itself be transmitted, or without being transmitted, may lead to various anomalies of growth and development. These latter are of great number, but among the most characteristic

* 'Arch. f. Gynæk.,' 1881, vol. xviii, p. 109 (from Ballantyne).

† 'Principles and Practice of Medicine,' edited by Dr. Pye Smith, vol. i, ed. 1, p. 578.

‡ *Loc. cit.*, p. 418.

are different forms of infantilism, general and local, though apparently almost all sorts of malformations and developmental anomalies are included in the long list which Ballantyne has drawn up.

It does not seem possible to say whether the toxin of syphilis or of wine is the more disastrous to the foetus. Ballantyne* in writing on the effect of alcoholism, says that E. Fournier† has shown that as with syphilis, so with alcoholism, the progeny is apt to exhibit structural anomalies, such as infantilism, multiple malformations (*e. g.* ectrodactyly, defect of occipital bone, hydrocephaly, cranial asymmetry, porencephaly and microcephaly). "This statement is simply the modern expression of a belief as old as the times of Hippocrates; and the deformed Vulcan was regarded as a result of Jupiter's drunkenness."

We have now seen that the three poisons, lead, syphilis, and alcohol, which are of most importance in giving rise to post-natal diseases of development, have also the most influence in producing pre-natal diseases of development. Of these three, syphilis and alcohol are of the greater consequence, because they are more prevalent. Further, the diseases started in foetal life are, roughly speaking, of the same order as those which originate in post-natal life, syphilis being almost universal in its manifestations, while alcohol shows a special affinity for the nervous and alimentary systems. Moreover, the foetal diseases which both these poisons generate are, for the most part, *defects* of development, such as general infantilism, microcephaly, hare-lip; whereas those which are produced in the later stages of post-natal life are of the nature of *senilism* or degeneration. This fact enables us to make another generalisation of great importance, to wit, *those agents which retard or arrest development during its progressive stages bring about degeneration or senilism during its retrogressive stages.*

But our comparison does not stop here. We can go further back, and trace the effect of the same factors, not only in facilitating degeneration and causing arrest of development, but in acting as destructors of early foetal life and as *preventers of conception*. In other words, they not only induce retrogression in the development of the completed human being, and delay or arrest the development of the half-finished product, but stop the evolution of the child at its beginning, and even sterilise the reproductive cells of the parent before they have had a chance of forming a

* *Loc. cit.*, p. 276.

† 'Stigmates dystrophiques de l'hérédosyphilis,' 1898, p. 318.

blastoderm. Spiegelberg says* that intra-uterine death may be due to an inadequate supply of nutritive material, dependent upon *malnutrition* of the mother and upon *syphilis*, *lead*, or other kind of poisoning. In this list we must undoubtedly also include *alcohol*. Lead is used deliberately as an abortifacient, though it has to be taken at the risk of producing serious bodily illness, insanity, or even death.† Syphilis also is exceedingly well known as a cause of abortion, but the responsibility of alcohol is not so widely recognised. Friedenwald‡ found, as the result of his experiments, that alcohol had a decided effect in bringing on abortion in rabbits, as well as in rendering them vulnerable to septicæmia. Of thirty-eight pregnant and alcoholic rabbits, twenty died from septicæmia following abortion, and nine more had frequent abortions. In only three did pregnancy go to term, but all the young died a few days after birth.

Both lead and syphilis lead to sterility, for both exert a direct disorganising action on the germ-cells.§ Alcohol also limits fertility, probably in part by its direct influence on the germ-cells, certainly by setting up or facilitating local diseases of the ovaries, Fallopian tubes and uterus, and equally as certainly by giving rise to insanity or other sterilising diseases.

There are also data which seem to prove that a decided drop in the birth-rate sets in during times of *great privation* and of intense *emotion*. Statistics show that famine, war, or a prolonged siege, like the siege of Paris, are all associated with lessened fecundity of the people affected. But in each of these cases other factors must be taken into consideration, as well as that of the direct influence of these causes on the rate of birth, considerably reducing their significance.

There can be no doubt that a remarkable consistency runs through the whole subject of pre-natal and post-natal errors of development. Not only are the causes of post-natal retrogression the same causes as those which at an earlier age check progress, but they also stop development at its source. Moreover, we have seen that causal influences are at work which spring from some family source, or from ancestral taints, so remote as to baffle all our efforts to detect them, and these hidden influences are probably even of more importance than are those which are not hidden. Such occult influences

* 'Text-book of Midwifery, Transl. New Sydenham Society,' vol. i, p. 497.

† See paper by Dr. Ball, 'Brit. Med. Journ.,' 1905, vol. i, p. 584.

‡ 'Journ. Amer. Med. Assoc.,' 1905, vol. xlv, p. 780.

§ Dr. Mott, "Heredity and Disease," 'Brit. Med. Journ.,' 1905, vol. ii, p. 1088.

are indeed present in all the varying forms of mal-development, no matter whether they affect the germ, the blastoderm, the embryo, the foetus, the post-natal child, the mature individual, or the individual in his retrogressive stages.

The way in which all degenerating agencies, including degeneration itself, lead along a road which is destined to end in sterility is, perhaps, best shown in the case of the most highly developed organs, seeing that in their case the contrasts during the process of deterioration are most obvious. "The hereditary psychoses, according to Morel, are communicated to the offspring always at an earlier age in each generation, and in a more severe form, and end by manifesting themselves at birth in the form of congenital idiocy. Idiocy is frequently associated with sterility, and thus the process of degeneration, though it may not be fatal to the individual, exterminates the degenerated stock by preventing its continuation." *

What is true of the degenerations of the cerebral organ is also true, in varying degrees, of the degenerations of all other organs in the body. They are all destined eventually to lead to their own automatic extinction by means of sterility.

* Tanzi, 'Text-book of Mental Diseases,' transl. by Dr. Ford Robertson and Dr. T. C. Mackenzie, 1909, p. 62.

VIII

THE DISTINGUISHING FEATURES OF THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT

The structural changes in the disorders of *growth* are quantitative, though there may be some incidental degeneration. Those of *development* are qualitative, and consist of a return to primitive simplicity. The connective-tissue cells, or fibroblasts, are distinctively constructive, polymorphonuclears defensive (phagocytic), and lymphocytes scavenging, reducing worn out or senile cells to their simple rounded state.

The functional changes of presenile degeneration are an exaggeration of those which are met with in normal old age, converted into the symptoms of disease by their incongruity.

I. Structural Characters.

THE changes which cells undergo when their growth is interfered with either in the direction of diminution or of redundancy have already incidentally been referred to, but a few more words must be said on this subject. In a general way an excess of growth of *single cells* consists in the simple multiplication of units, but along with this simple overgrowth there always goes a certain amount of incidental degeneration. In this respect there is a vast difference between different tumours. At one end of the scale the cells correspond very closely indeed with the cells of the normal tissue from which they spring. This is the case, for example, with some fatty and fibrous tumours, which so closely resemble normal fat and normal fibrous tissue respectively that both naked eye and microscopical examination show hardly any difference between them. In fact they both shade off by imperceptible degrees into ordinary tissue. At the other end of the scale we meet with innocent tumours in which the cells have undergone very obvious degeneration. Such, for example, are certain tumours of granulation-tissue, bleeding polypi of the nose, and, perhaps, some recurrent fibromata. All these are on, or very near, the borderland between innocence and malignance. But though taking an intermediate position, they serve at the same time to emphasise the distinction which has been made between a cell-growth and a cell-degeneration. For the more

nearly their structure corresponds with the tissue from which they arise the more innocent are they, and the more their cells differ the more nearly do they approach malignance. In other words, the more positive we are that a tumour is a simple *growth* the more easy do we feel in regard to its consequences, and the more *degenerate* its cells appear the more do we suspect its evil qualities. It is necessary to reiterate that the essential difference between innocence and malignance lies in the answer to the question whether the cells have simply grown, or have undergone developmental changes.

Very little need be said on the subject of the corresponding diseases of *entire organs*, for the changes which indicate degeneration are just as important in distinguishing between overgrowth and premature senility of organs as they are in distinguishing between innocent and malignant accumulations of cells. An organ which has undergone simple overgrowth, or "hypertrophy," as it is usually termed, has undergone a *quantitative* change, and its structure is hardly to be distinguished from that of the normal organ. On the other hand, the organ which has undergone the changes characteristic of senilism has altered in *quality*: it has degenerated. But just as in the case of innocent growths a certain amount of degeneration occurs incidentally, so is it with the overgrowths of organs, and this incidental degeneration sometimes goes to such lengths that in a given case it may not be easy to say from the structure whether the organ is more overgrown or more degenerate. This is the case, for example, in some instances of thyroid enlargement and of giant hand. The two processes of overgrowth and of degeneration merge one into the other to form "degenerative hyperplasia."

The nature of degeneration.—It is evident from what has been said that the view of degeneration which is commonly held must be put on one side. We have nothing to do with fatty, granular, lardaceous, or pigmentary changes in themselves. These are mere evidences of decadence and decay, and may or may not signify degeneration in our meaning of the word. In fact we must recognise that though the word "degeneration" is used for certain internal changes which are more or less destructive in nature, it is now applied to the whole process of which these cellular changes are but some modes of its expression. By degeneration we mean retrogression—backsliding. It is a reversal of the process of ascending development, and the signs of reversal consist in a return of the cell or tissue to a simpler condition. This simplification is accomplished by peripheral decay of the cell; by a process of centri-

petal phagocytosis, which so wears it down that its peculiarities of form are destroyed; and by proliferation and reconstruction of tissue on a simpler basis. Hence fatty degeneration of a multipolar nerve-cell or of a liver-cell may result in the complete loss of its special characters, so that the processes of the one and the angles of the other decay and undergo absorption, leaving a more or less rounded cell with a nucleus; and continuing, perhaps, until the nucleus is left almost bare, stripped of nearly the whole of its investing protoplasm, constituting one form of the so-called "inflammatory" cell. Further, such generation backwards or downwards may start on a lower plane. If, instead of taking for our example a highly developed nerve or liver-cell, we begin with a connective-tissue cell, the simplification or retracement will evidently not show the same stages, and the only evidence that such a retracement has taken place will consist in a transformation into an aggressively proliferating embryonic cell—round, spindle- or oat-shaped—which we know as a sarcoma cell. As a third possibility we may have both these evidences of degeneration running concurrently, or one after the other, so that mingled among cells which have been reduced from a higher to a simpler state are other cells which have always been of low development.

The versatility of cells of low development is very great, and much may be learned of the process of *degeneration* by studying what goes on in *regeneration*. Dr. Maximow* says that connective-tissue cells (fibroblasts) are the ultimate builders of new connective tissue, but that they are preceded by lymphocytes and by polymorphonuclear cells, which pave the way for the fibroblasts. Some of the connective-tissue cells turn into lymphocytes, but most of the lymphocytes have migrated from the blood-vessels. There seems to be as much diversity of function among the more primitive cells of the body as there is among the soldiers of an army in time of war. And just as in certain emergencies soldiers have to put their hands to whatever comes uppermost in the order of events, so also the primitive cells, though with definite allotted functions, have to accommodate themselves to varying circumstances. Connective-tissue cells are in the first place constructive, but, if occasion arise, they act as phagocytes. So also the polymorphonuclear leucocytes, though distinctively the soldier-cells of the body, are also capable of forming fibrous tissue. Perhaps the lymphocytes are the most versatile of all, for they both act as phagocytes in clearing up waste or effete material of all kinds,

* 'Experimentelle Untersuchungen über die entzündliche Neubildung von Bindegewebe,' Von Dr. Alex. Maximow.

and are also constructive, though the tissue they form is not lasting, but is soon replaced by the more permanent work of the fibroblasts.* Of all these cells "the smallest lymphocyte forms are most abundant in the specially chronic processes—in fibrotic changes."

Nothing can better illustrate the structural features of presenile degeneration than the cirrhotic liver. The local changes in this disease are exactly the same in kind as those which we have already seen in the normal fibrosis of old age, and consist in the main of molecular decay of liver-cells and their gradual absorption by phagocytosis. The molecular decay (granular and fatty changes) is chiefly peripheral, and the absorption of the decayed material necessarily results in the simplification of the cell, so that the polyhedron becomes worn down into an irregular cuboid and that again into a rough sphere. Finally nothing but the nucleus is left, with perhaps just a vestige of cytoplasm clinging to it. On this road to ruin the cell evidently retains its functional activity, for in the midway stages the cubical cells often arrange themselves into the semblance of ducts, as if they were starting life over again and had arrived at the tubular stage of development. So also when these duct-like cells have further degenerated into round cells, these round cells, as befits their shape, apparently take on the work of fibroblasts, and form new fibrous tissue.†

The part played by the phagocytes in this retrogression is entirely beneficent. They clear away the effete cytoplasm from the circumference of the cells so as to leave them unhampered by the dead products of their own degeneration, and this work accomplished, they apparently help to fill up the gaps which have been left by the shrinkage of the liver-cells. They finish their career by turning into fibrous tissue.

We are now in a position clearly to differentiate between the structural changes which take place in (1) regeneration, (2) inflammation, and (3) presenile degeneration, or senilism.

(1) *Regeneration* is purely constructive, and is in the main the work of embryonic connective tissue, or *fibroblasts*.

(2) *Inflammation* is the response of the tissue to injury and is therefore a defensive process. The cells engaged are mainly *polymorphonuclears*.

(3) *Senile and presenile degeneration* (senilism) consist in a reversion to a prior stage of development, and are consequently charac-

* Dr. Muir, 'Brit. Med. Journ.,' 1904, vol. ii, p. 585.

† Hamilton's view, but denied by H. D. Rolleston, MacIntyre, and other authorities.

terised chiefly by the presence of embryonic cells, and of phagocytes of the scavenging order. The characteristic cells are *lymphocytes* and *fibroblasts*.

Emphasis must be laid upon this last paragraph. It will be seen that we should fall into a capital error if we regarded the new fibrous tissue as of fundamental importance. The fibrous tissue is in fact a mere incident in the process of deterioration. The essential constituent of all presenile tissues is the returned embryonic cell, or, at any rate, the cell which is in process of reversing its development.

We now see that the structural changes which characterise premature senile degeneration of an organ, or senilism, do not differ, except in degree, from those which constitute ordinary senility. In fact the description which has just been given of the changes met with in senilism are little more than a repetition of those which have already been detailed in the chapter on normal old age (p. 17).

Functional Characters.

The functional characters, or symptoms, of any disease of development must of necessity correspond with the structural characters. In normal old age gradual functional deterioration takes place, and this functional deterioration keeps pace with, and is the direct expression of, the anatomical deterioration. Hence, the kidney affected with premature senility gradually lessens its output of urea, and the liver affected in the same way shows progressive diminution in the secretion of bile.

But no organ shows the functional consequences of degeneration better than the brain, for the higher the development of an organ the more conspicuous are the changes which mark its retrogression. Hughlings Jackson, writing so long ago as 1868, pointed out that : "In the degeneration of this system the higher functions, those more complex, specialised, and voluntary, disappear more quickly than the lower, simpler, less specialised and more automatic functions."*

The only differences between the symptoms which mark the decline of an organ in a degenerative disease and those functional characters which characterise its decline in normal old age consist in their greater irregularity and more pronounced degree when the degeneration is premature than when it is normal. They are more pronounced because the contrast between the diseased organ and the normal remainder of the body accentuates the local weakness.

* Hughlings Jackson, 'Med. Times,' 1868, vol. ii, p. 178.

They are more irregular because abnormal presenility is always a more partial process, affecting one organ or one department of an organ far more than another. Hence, while in normal senile decay of the brain there is a gradual deterioration all round, in the abnormal the deterioration affects some function far more than it does others. Normal old age is a uniform process which reaches its limit in general weakness, or dotage. But the more partial degenerations of presenility, or senilism, are manifested by such diseases as dementia paralytica, paralysis agitans, when it affects the brain, and tabes, lateral sclerosis, disseminated sclerosis when it affects the spinal cord.

In normal senility the degenerated organ is more in harmony with its surroundings. In abnormal senility it is adversely situated in respect to its surroundings. In the one the symptoms are gradual in onset and mild in degree, such as is becoming to the terminal period of life; in the other they are more abrupt in their appearance and violent in the event. The manifestations of the one consist in an orderly procession of retrogressive changes. The manifestations of the other are more or less disorderly and constitute the symptoms of disease.

IX

DEGENERATION; INFANTILISM; SENILISM; ASSOCIATION OF CHARACTERS

Degeneration is either racial or individual. Racial degeneration is due to disuse or abuse, and is an essential element in the scheme of evolution. Individual degeneration is either *molecular* or *senile*.

Infantilism is not merely delayed development. Certain stages of development are left out, so that life is shortened rather than prolonged.

Senilism also is more than premature old age. It is a true disease, the disease condition being constituted by the premature senile decay on the one part, and the normal state of the environment on the other.

The stigmata of degeneration may all be included under the heads of defects or excesses of growth or development. A growth or developmental disease of one organ is prone to be *associated* with some similar disease of another organ. This is the result of *correlation*, and has an important bearing upon the diagnosis and pathology of the correlated disorders.

THREE words have been made use of on different occasions in the preceding pages, each of which requires some fuller explanation. These words are "degeneration," "infantilism," and "senilism."

The first requires defining because its meaning is diffuse and is applied to many different conditions, and the second and third demand consideration because they are as yet unfamiliar.

Degeneration.

The word degeneration (*degenerare*, to become unlike its kind) is applied to "a change of condition, but always for the worse."* We meet with it under at least three different circumstances. Degeneration may be classified as follows:

1. Phylogenetic or racial.
2. Ontogenetic or individual.
 - (a) Molecular.
 - (b) Senile.

* Hoblyn's 'Dictionary of Medical Terms,' by Dr. Price.

1. *Phylogenetic or Racial Degeneration.*

This form of deterioration arises from either disuse or abuse. The part or individual affected does not reverse its evolution, but undergoes atrophy and gradually declines until it disappears. The process is, therefore, not primarily one of evolutionary old age, but is in the first place a form of infantilism and only secondarily a degeneration. It is an integral and essential part of the scheme of phylogenetic progress. "Degeneration and progress will appear as the two sides to one whole, or as two aspects of the same evolution, and it will be seen that all progress must necessarily be attended by degeneration."*

In writing on some examples of this form of degeneration Ray Lankester says: "Degeneration may be defined as a gradual change of the structure in which the organism becomes adapted to *less* varied and *less* complex conditions of life,"† and gives, as an example of this form of degeneration, the ascidians, which he regards as degenerate Vertebrata. Certain negro and other savage races are also degenerate, for they show evidences of having descended from superior ancestors. As applied to such instances as these, the word is used to express an idea which is the exact contrary to evolution, and is, in fact, devolution.

2. *Ontogenetic Degeneration.*

(a) ***Molecular degeneration.***—This consists in granular, fatty, mucoid, lardaceous, pigmentary or calcareous changes in the protoplasm of the cell.

Molecular degeneration may take place in a cell to a degree which markedly interferes with its usefulness without producing changes perceptible under the microscope. Or perhaps the only evidence of deterioration may be an increase or decrease in size, some impairment of staining properties, or of some function, such as that of secretion, phagocytosis, amœboid power. Lessened resistance to injury is also a sign of this form of deterioration, as when a cell is too easily crushed by the pressure of a cover-glass.

(b) ***Senile degeneration.***—This form—the deterioration produced by age—need not be specially defined here because such definition is carried out pretty thoroughly in the rest of the book. Neverthe-

* Demoor, Massart and Vandervelde, 'Evolution by Atrophy in Biology and Sociology,' transl. by Wm. Mitchell, p. 22.

† 'Degeneration,' p. 33.

less, some reference must be made to the words "infantilism" and "senilism" which occur so frequently. Nothing seems more outside the scope of our present subject of senile degeneration than that of infantilism, yet it is so closely allied to premature senility and is so often its precursor that it is fitting that it should be considered at the same time. Moreover, both of these states are closely allied forms of deterioration, and for that reason alone cannot be dissociated.

The Terms "Infantilism" and "Senilism."

For the use of the word "infantilism" we are indebted to the French, who applied it to delay or arrest of development of the whole body during the progressive stages. It is now recognised as an accepted term. And if "infantilism" is to form part of our medical nomenclature the word "senilism," as applied to the opposite disorder of the regressive periods of development, becomes inevitable. But one of the chief objects of this book is to show that there is complete uniformity between the developmental disorders of the three system units of the body—that is, between cells, organs, and the entire man. However widely the manifestations of these disorders may differ in detail, they are alike in principle, and it is of the first importance that this identity should be expressed in their nomenclature. Hence, to be consistent we must make use not only of the word "infantilism," but of "senilism" as well, and not only infantilism and senilism of complete human beings, but of cells alone and of organs alone.

Another advantage to be derived from the terms "infantilism" and "senilism" is so decisive as must alone be sufficient to justify their use. The descriptive phrases, "defective development" and "premature old age," are applicable to their respective conditions, however slight or however pronounced they may be. They apply equally to the normal and to the abnormal, whereas when we speak of "infantilism" or "senilism" we refer to the abnormal only. Indeed, we may go further and regard them as indicative of actual disease, or, at any rate, of that which is closely akin to disease. These terms are, therefore, not only more convenient, but more accurate and more precise.

If this view be correct it is obvious that we ought fully to understand what we mean by "infantilism" and "senilism."

By *infantilism* we do not mean to imply that the tide of development is merely delayed. If such were the case, the life of, say, an

organ might be as vigorous, or even more so, than that of the rest of the body. The organ, indeed, would flourish in perpetual youth. Such a part might be abnormal, but would not be morbid. The mark of disease is shown by the fact that such delays or stoppages of development show a very distinct tendency to end in premature degeneration. In other words, the three processes of growth, development and nutrition are prone to become dissociated.

It must be evident that if old age be a return to an infantile condition, a state of abortive infancy will be peculiarly liable to terminate in premature old age. If the road to the grave be marked off into seven stages, the cell, organ, or individual that never reaches maturity, but stops short at an earlier age, does not thereby live a prolonged life, but has in reality taken a short cut to old age. Instead of reversing the whole cycle of life the reversion begins before maturity, for some of the stages are left out, and it follows that the second infantile and the embryonic stages are reached much sooner. The condition of infantilism consequently means an increased liability to premature old age and senilism. *Cells* which are arrested in the course of their development and are embedded among the normal cells of a mature organ are peculiarly prone to undergo the senilism of cancer.

Organs, like the thyroid gland, testes (in such cases always misplaced), heart, lungs, pancreas, which never develop properly, but remain small and immature in a mature body, usually undergo the premature degeneration or senilism of fibrosis. The individual boy who remains small and puny and never develops into a *man* is not, therefore, set aside for a life of patriarchal dimensions, but, like the aborted apple, is prone to ripen early and to drop while his fellows are yet green.

After the same fashion one is at first tempted to regard *senilism* as a mere exaggeration of normal retrogressive development. It is recognised that organs do not always age at the same time. What, therefore, can be more likely than if an organ become senile long before its time, while the rest of the body is still vigorous, it should simply show the characters of old age to an exaggerated degree? That is to say, that as normal senile decay is manifested both by the reversion of cells to an earlier and simpler condition and by an influx or proliferation of embryonic cells, so this premature old age, or senilism, would be manifested by a gross exaggeration of these two series of changes. An organ so affected would show simplification of cells of high type, with proliferation of cells of lower type, and these characters would become more and more exaggerated the

longer the individual lived. Now this is exactly what happens in senilism, for senilism is just such a caricature of normal old age. But here, again, plausible as this view may seem, it does not go far enough, for it does not carry us beyond the bounds of healthy but hastened development. We must fully realise that senilism is not an acceleration pure and simple, but is a true disease, for those organs which naturally become senile while the body is still young do not behave like organs affected with senilism. The uterus at the menopause does not usually fill out with quantities of young cells, but a shrinkage takes place from the beginning. There is a vast difference between the thyroid gland which decays in a normal way and the thyroid gland which is affected with senilism. The normal gland rapidly shrinks, until, in a few years, hardly a vestige of it remains, only a few shreds of fibrous tissue marking its position. But the thyroid gland affected with the disease senilism is often both enlarged and persistent. It is swollen with quantities of new tissue, and may become in this way far larger than the healthy gland at its biggest. Hence, senilism is a true disease, for though it has its basis in natural old age, that natural process is not only accelerated, but perverted. In short, not one, but two factors are requisite in order to constitute a disease of development, the one being the abnormal state of the organ or cell or man, and the other the normal state of the surroundings. It is the action and reaction of the one upon the other which constitutes senilism, and it is the want of action or inaction of the defective part or man, together with the activity of the surroundings, which constitute infantilism.

The Stigmata of Degeneration.

We must now refer to certain abnormalities of scattered distribution which have received much attention of late, and are, perhaps, not even now estimated at their proper value. These are the so-called "stigmata of degeneration." They are, in fact, perversions or alterations of form or function, sometimes of growth, at others of development, pre-natal in one case, post-natal in another, expressing themselves now in the direction of excess and then in that of defect. Generally speaking the expression is used for the less definite or minor degrees of perversion, and is not so often applied to those great and well-defined perversions which are recognised and classified as distinct diseases; though it really embraces all forms of regressive abnormality, big and little.

When we see an individual with an organ or part of a size not

according to his needs, the want of correspondence attracts our attention. It is incongruous and constitutes a deformity, and such deformity is prone to be associated with other bodily, mental, or moral obliquities. We therefore do right to term it a mark of degeneration. Thus some members of the family of the Philips of Spain were distinguished by the ugly projection of their mandibles and, to a like extent, by certain undesirable moral qualities which had a very potent influence in contributing to the downfall of the Spanish nation. Nowadays, those who possess such characters as these would be termed "degenerates" or "stigmatics."

Most of the stigmata of degeneration consist either of redundances or of defects, as when the lower jaw is too small or too large, or the upper jaw is curtailed or is too long, or the nose is manifestly too big or too short for the face. The effect of these abnormalities is to produce a noticeable blot on that even disposition of the features which is so essential both to perfect function and to a pleasing appearance. Hence, if the upper jaw be overgrown, the type of physiognomy is that of a horse. If the lower jaw be enlarged it looks heavy and underhung, or the face is hatchet-shaped. If, on the other hand, the upper jaw be defective, the countenance has an unpleasing, crushed appearance, and there is an undue relative projection of the forehead and mandible. Other parts of the face or of the body or the limbs are liable to similar irregularities. Sometimes the ears are large and coarse, or, on the other hand, are too small, or the lobes are defective. So also with the hands or the feet. The upper or lower limbs may be too big or too little, too long or too short. The nails may be defective, easily breaking off, so that the frayed ends are often nibbled away or picked with the fingers. Sometimes the knuckles are too big, so that the hands look clumsy and coarse.

Often the stigmata of degeneration consist rather in disproportionate growth than in any very definite over- or undergrowth. In reality this is a distinction without a difference, for if the ear be badly formed so that there is hardly any helix, or so that Darwin's point projects unduly, the deformity is still one of excess or defect. So also when the stigma consists in some lop-sided appearance of the face, in a too sloping forehead, or in an unpleasing projection of the occiput, the effect is always produced by disproportionate growth, that is, by over- or undergrowth.

It is not necessary to enter into particulars of the many different marks of degeneration. It is sufficient to say that among them are included all forms of insanity and crime, prostitution and other kinds

of sexual perversion, inebriety, epilepsy, genius, idiocy, deaf-mutism, colour-blindness, "idiopathic" sterility, obesity and emaciation, and all pre-natal abnormalities.* They may be anatomical, physiological, psychical. It is important to recognise that among the stigmata of degeneration we must include not only ill development of the sexual organs, but inborn lack of fertility. Indeed, this is one of the most important of the stigmata, for it implies not only the deterioration of an important function of the individual but is a grave indication of racial impairment.

Significance of the Stigmata of Degeneration.

The question which now crops up is one of immense practical importance. If these and similar irregularities constitute marks of degeneration, we apparently have it within our power to judge the character of our fellows off-hand, without having to go through the tedious and often expensive process of finding them out by months or years of experience. In fact, if we accept the conclusions of some anthropologists, we must recognise that certain individuals are "ear-marked" almost from birth, and are set apart as pre-destined to become the good-for-nothings or criminals of society.

"But thou art neither like thy sire nor dam;
But like a foul misshapèd stigmatick
Mark'd by the destinies to be avoided,
As venom toads, or lizards' dreadful stings."

"King Henry VI," Act. ii, Sc. 3.

Some writers have even gone so far as to suggest that such degenerates should be given some form of happy despatch, or should, at any rate, effectually be prevented from handing down their undesirable qualities to their descendants. But when we come to inquire into the nature of the so-called "marks of degeneration," we must arrive at a very different conclusion.

Thus we cannot draw a line between abnormalities of various kinds so as to put all the bad on one side and all the good on the other. Each mark of degeneration must be accepted on its own merits, and it is neither just nor scientific to regard a man as lacking in moral control because he has a "degenerate" ear or head. To do so is to fall into the error of phrenology, for it is just as illogical to draw unfavourable conclusions of mind or morals from the shape of an ear or the size of a nose as from the prominence of certain "bumps" on the skull. Indeed, quite as often as not an exaggera-

* See classification on p. 38 of Dr. Talbot's work on 'Degeneracy.'

tion or defect of some external feature is associated with unusually good mental or moral qualities.

According to the usual acceptation of the word, Byron and Shelley were both degenerates: Shelley's most striking physical peculiarity was his little, round, bullet-head, which he loved to expose to the heat of a fire; and Byron was club-footed, a hypochondriac, and defective in moral perception. So also, by the same token, must we regard Gladstone as a degenerate, for he was an intellectual giant, was possessed of a brain which was not only abnormal in size, but behaved abnormally in continuing to grow long after brain growth has usually ceased. Perhaps nothing shows up his abnormality more conspicuously than the fact that he alone and none of his forbears could be regarded as distinguished, and that his eldest son died from a tumour of the brain.*

This brings us to the point that as development is an affair of the family and of the race as well as of the individual, so also the characters which indicate "degeneracy" can hardly be confined to the individual, but must be shown also in the character of his offspring or even in his inability to produce offspring. Thus John Howard seems to have been a man who was mastered by an overwhelming idea. He laboured so persistently on behalf of poor prisoners, and to such purpose, that his name now stands out almost as conspicuously in the domain of philanthropy as does the name of Napoleon in that of military science. Yet Howard's only son was hopelessly depraved, and, so far as such a case can carry us, he must be considered as evidence of a noble want of balance on the part of his father. So also Julius Cæsar was a "degenerate," for he was liable to epileptic seizures, and his direct descendants were amongst the worst and most unbalanced of all rulers. Lombroso† has indeed proved up to the hilt that genius, the "divine infirmity," is itself semi-morbid, and occurs so often in association with malformations of body, mind or morals that it must be placed with them in the same category.

Furthermore, there are but few who cannot call to mind some great mathematician, divine, linguist, philanthropist, among his acquaintances, remarkable not only for his special accomplishment, but also by reason of some oddity of dress, person, or manner—some eccentricity, or mental or moral astigmatism—which serves for the amusement of his friends, the wonder of his acquaintances, the gibes or slander of his enemies.

* See an editorial on "The Fallacy of the Criminal Type," 'Brit. Med. Journ.,' 1900, vol. ii, p. 980.

† 'The Man of Genius,' Contemporary Science Series.

Evidently the terms "stigma" and "degeneration" are capable of serious misuse, and we cannot be too careful in their application. To stigmatise some people as degenerate because of the possession of some inherent defect of structure or character may constitute an abuse of language or a slander. A man may have marks of degeneration in the form of malformed ears, colour-blindness, or even of such moral blindness as renders him unable to distinguish between his own property and the property of others: yet at the same time, he may be a man of wide benevolence, a musical prodigy, or show a remarkable aptitude for languages.

We cannot do better than close these remarks on stigmatism with the words of Dr. Tredgold, who, in his luminous work on 'Mental Deficiency,'* sums up their value as follows:

"It has been remarked that similar anomalies occur in persons who are not otherwise abnormal. Nevertheless, it is abundantly clear that they are far more numerous in neuropaths and in aments than in the general population. Further, that their number and severity are, on the whole, directly proportionate to the degree of defect. Whilst, therefore, the presence of a single anomaly is of little or no diagnostic importance, the presence of two, three or more, is of considerable significance as an indication of mental defect."

All the stigmata are in one sense indications of degeneration, for though themselves often errors of growth rather than of development, they are associated either with defective development or with premature old age, and are harbingers or concomitants of degeneration.

It is evident that though the word "stigma" is as a term of opprobrium by no means desirable, yet the phrase "stigmata of degeneration" is, with some reservations, on the whole not inappropriate.

In future when degeneration is alluded to it will for the sake of clearness be termed "molecular" if applied to protoplasmic decay, "racial" or "phylogenetic" if applied to evolutionary changes, and the word "degeneration" alone will be reserved for the descending or regressive changes which take place in old age, normal or premature.

Association of Characters: Correlation.

Defects of the cerebral apparatus so often occur among the stigmatic that the stigmata are usually regarded as the direct conse-

* 'Mental Deficiency' ("Amentia"), 1908, p. 80.

quence of the brain defect. But it is probable that this generalisation is a little too sweeping. It is only to be expected that when development becomes perverted the most highly organised parts of the body should suffer most often. But it is seldom that any anatomical relation can be detected between the site of the brain defect and of the bodily perversion. All that can be said is that the most common accompaniments of the cerebral defect are alterations in the configuration of the cranium or face. But these are parts which come into close anatomical relation with the brain under normal conditions, and it seems highly probable that they share in the vicious development of the brain by virtue of this relation. They are, in short, *associated* or *correlated* with one another, and are not in the relation of cause and effect.

That this is the true state of affairs is, moreover, suggested by the way in which the bodily or facial stigmata sometimes occur apart from alterations of the brain and *vice versâ*.

Now, this fact of association or correlation is of great importance, not only for its own sake, but because of its bearing upon the nature of the correlated conditions.

It has been noticed by plant breeders that "correlated variability" is not an uncommon feature in plant life, and one to which all plants are liable. "As soon as a plant deviates from its type it will be disposed to do so in more than one character. This rule holds good for race and casual abnormalities, as well as for the more normal, so-called fluctuating deviations from the type. Useful qualities are subjected to it, as well as those practically useless marks, which are usually studied merely on account of the valuable indications they so often give for comparative science."*

Plants, therefore, as well as animals, are liable to the "stigmata of degeneration," and these also are grouped together by correlation. Moreover, it is a matter of common observation among gardeners that the more highly cultivated the plant the more liable is it to vary or "sport," so that whereas the common perennial sweet pea remains comparatively stable in form and colour, the sweet peas of the prize winner, delicately nurtured upon rotting leaves and pigs' dung, throw out crop after crop of glorious bloom, lavishly sprinkled with "sports."

It would be a mistake to suppose that correlation comes into play only during the rising tide of development. We see that hare-lip is associated with cleft palate, with supernumerary auricles, or with

* Hugo de Vries, 'Plant-Breeding,' Chapter V, "The Association of Characters," p. 290.

some other pre-natal abnormality, but we are apt to overlook similar correlations which occur in post-natal life. Thus, the occurrence of cirrhosis of the liver, or of arterial sclerosis, with renal fibrosis, is just as truly the result of correlation as when an infantile kidney is found associated with defective development of some other part of the urinary tract. This is but one of many examples of the rule that organs which are accustomed to act together are liable to degenerate together.

Sometimes the organs stricken with infantilism or with degeneration are obviously correlated, as in the cases just given; at other times the associated diseases occur in organs apparently so far apart in regard to structure or function that it seems impossible to trace any connecting link of correlation. At the same time it must be recognised that correlation may occur under circumstances in which, at first sight, any affinity seems out of the question. Dr. Morrison states that when travelling in some out-of-the-way part of China he was once stopping in a guest-house, and was greatly disturbed in his sleep by the braying of a donkey. On complaining of the nuisance he was interested to observe that his Chinaman host, without saying a word, slipped out of the room with a brick, and presently returned to go on with his occupation. From that time forth there was no more braying. Dr. Morrison, whose curiosity was aroused, demanded an explanation of the mystery, and was taken by the Chinaman to see for himself how the marvel had been brought about. It seems that each time the donkey had raised its voice it had also lifted its tail, and the Chinaman, noticing the correlation, had so weighted the tail that the mechanism of braying was deranged and the depressed animal was constrained to remain silent.

This illustration serves two purposes. We see, in the first place, that organs may be as widely separated as it is possible for them to be, and may yet work together. At the same time the correlation may be so intimate that when, from any cause, the function of the one is stopped, the function of the other cannot continue. It may happen, moreover, that the derangement which brings about this result is not of the chief or primary organ, but of the inferior, or secondary organ. We shall, in fact, later on, come across many examples serving to show that in their relations one with another the disorder of one part of the body may cause such sympathetic disorder of another part as to remind one of the way in which a dog not only wags his tail but the tail wags the dog.

A good example of these interchanging relations is furnished by

the effect of general old age in giving rise to local senilism of some particular organ, and of the way in which premature degeneration of an organ sometimes brings about general senile decay. Thus, we all recognise that general senile decay is an important factor in the production of cancer, or of other forms of presenile degeneration. But it has again and again been noticed that cancerous, or other local degeneration, may cause premature old age of the body as a whole. At any rate, senility is, in some cases, the first symptom of there being something amiss. It may come on long before the disease is manifested by pain or other derangement of the particular organ at fault. Hence, when a patient in his fifth decade complains of debility, wasting, and of general impairment of vitality, as if he were "breaking up," or becoming an old man, our first thought is that he has either cancer or fibrous degeneration of some organ. Moreover, even if we fail to find any sign of local senilism we are by no means surprised when, a few weeks afterwards, the same patient appears before us with definite indication of cancer or fibrosis. In such cases as these it is the custom to account for the general senility by supposing that some enzyme or decomposition product has been formed and is slowly intoxicating the body. These symptoms may, however, occur long before ulceration sets in, or before, indeed, there has been a single symptom suggestive of interference with the function of the particular part affected.

This is but one example of the possible influence of correlation. We shall find that in other cases we can speak still more positively of its effect in causing the breakdown of associated organs. Correlation, therefore, will frequently be alluded to as evidence in the ensuing pages.

Correlation at times occurs, not among the organs of the same individual, but of the same family. This *familial correlation* is no doubt capable of explanation by Mendel's principles. An instance, recorded by Dr. Kiernan (p. 73), has already been given; and also another, almost equally remarkable, by Sir Clifford Allbutt. We may now refer to a third, perhaps still more striking, given on the authority of Dr. Silvestri.* In describing a case of myotonia congenita, he says that the eldest brother was born with myotonia congenita, and that he partially recovered, but afterwards presented symptoms typical of Erb's juvenile paralysis. The second and third children were rickety, and the fourth was affected with myxœdema. This was not all, for of the previous generation the mother's brother died from Addison's disease, one of her sisters from progressive

* 'Gaz. deg. Ospedali,' 1909, Anno xxx, N. 55, p. 577.

muscular atrophy, and the mother herself was affected with osteomalacia. Here we have such a cluster of diseases on the same stem, most of them developmental and of such an unusual kind, that coincidence is out of the question. It seems clear that some kind of transmutation must have been at work, whereby correlated diseases were transmitted instead of diseases of the same kind. The subject is not one of which we can as yet write more definitely; it will again be alluded to under the heading of "Mendelism."

Generally speaking, the correlation which is of most importance is that which "involves the organ of sex and induces sterility. Experience has shown that in plants that have suddenly varied the power of persistence is diminished."* In other words, *a major or "saltatory variation arising from internal causes" (de Vries) makes for sterility.* Moreover, as we shall see later on, this rule is true of animals as well as of plants. No man or woman becomes affected with presenile variation of any organ, such as the liver (cirrhosis), kidney (Bright's disease), red blood (pernicious anæmia) without risk of loss of procreative power. General presenility is obviously a sterilising disease, and when we come to the subject of general infantilism we shall find that this, too, is liable to end in the blind alley of sterility. It is also highly probable that the subjects of cell senilism (cancer) are, generally speaking, of deficient sex capacity, though there may be many exceptions.

* Prof. Weismann, 'The Selection Theory.'

X

ORIGIN OF THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT; VARIATION

A disease of growth or development is necessarily a biological process in the first place, for its manifestations (symptoms) are invariably based upon physiological precedents. Its origin cannot be accounted for solely by the influence of toxins or other contemporary causes. There is another factor to be considered, and this proceeds from causes in action in remote evolutionary time. This second factor is termed *variation*.

Variations are of two kinds—minor and major. Diseases due to *minor* variation are partly the result of contemporary influences (toxins, etc.), and partly of impressions derived from bygone ages. Those due to *major* variation are solely the result of impressions of the past. Each may be either progressive or regressive, according as the genealogical event improved or retarded evolution. Variations are either physiological or pathological; physiological if in keeping with the normal customs of the body; pathological if they outrage those customs by going to extremes. The diseases of growth and development are eventually pathological, for they are variations of physiological conditions, unnaturally defective or carried to an equally unnatural excess.

Adaptation is the faculty whereby an organism adjusts itself to its circumstances. It supplements and facilitates variation. Variation forms the basis or substance of a new character, adaptation rounds it off, fitting it to the vicissitudes of a changing environment. Both play their part in the production of diseases of growth and development, sometimes the one being the more important factor, sometimes the other.

Rhythm economises effort, by rendering frequent repetition of a stimulus unnecessary. It may be *seasonal*, accounting for diurnal alternations of rest and activity, for mensal periodicity, and for certain annual changes. The occurrence of the changes of life is due to rhythm, and so also is variation, progressive and regressive. Memory and habit are also the result of rhythm. *Disorder of rhythm* occurs in epilepsy, migraine, fever, spermatorrhœa.

Heredity.—Acquired characters are not transmitted, though certain agents such as syphilis, alcohol, lead, are capable of directly affecting the germ-plasm. *Mendel* reduced the previous chaos of theoretic heredity into order by showing that the transmission of a character could be traced with mathematical accuracy. His formulæ account for the seeming disappearance of characters, for reversions, for sterility, and for familial and transforming heredity.

REFERENCE has been made to some of the causes of the disorders of growth and development and occasion taken to point out that they only partly account for these disorders, and that in some cases there is no discernible cause.

Evidently if we leave our subject at the stage to which we have brought it, a very important part will have been omitted. To render it more complete we must find an explanation both for the occurrence of idiopathic (spontaneous) forms of disease, and for that cryptic element which exists even in diseases of known ætiology. Thus, for example, we cannot very well pretend to deal with the subject of the diseases of liver development and leave out of consideration the origin of cirrhosis. We know that ordinary cirrhosis is partly caused by alcohol and partly by some other factor which is even more important than alcohol. We also know that some cases of cirrhosis, particularly of "hypertrophic" cirrhosis, may be solely the outcome of this mysterious hidden factor. It is now our duty to enter into the subject of the nature of this latter. To do this we have to go back to the past stages of our evolution.

Under normal conditions there is in all living organisms a constant tendency to diverge from the ordinary narrow paths of development. Such "variation" is to all appearance automatic; but though seemingly spontaneous, innate and inevitable, it is capable of being directed. In other words, while variation is intrinsic, in the first place, its manifestations are largely dependent upon extrinsic conditions. It follows the path of least resistance, or is changed from a latent into an active condition by favourable circumstances.

Variations, moreover, are themselves variable, some being more pronounced than others.

The existence of minor and major variations was recognised by Darwin, who was disposed to regard the former as the only variations of use in the origination of species.* Galton, however, contended that Darwin was at fault in this respect, and that the occasional production of "sports" is of more consequence than the frequent changes of slighter degrees of variation. Professor Bateson

* Ten years after the publication of the 'Origin of Species' a Mr. Bennett and the Duke of Argyll contended that the very title of the book was a misnomer, and that "the real origin of species is that spontaneous tendency to variation which has not yet been accounted for." Dr. Alfred Russell Wallace replied in 'Nature' that "a species is an organic form (or group) which, for periods of great and indefinite length, as compared with the duration of human life, fluctuates only within narrow limits. But the 'spontaneous tendency to variation' is altogether antagonistic to such comparative stability, and would, if unchecked, entirely destroy all species." This reply met with warm approval from Darwin ('My Life,' Alfred Russell Wallace, vol. ii, p. 8; see also "Method of Organic Evolution," by the same author, 'Fortnightly Review,' vol. lvii, n.s., 1895, p. 211). On the other hand, Huxley, in his essays on 'The Perpetuation of Living Beings' and 'The Conditions of Existence,' fully recognised the importance of spontaneous (major) variations in the formation of permanent species. Haeckel ('General Morphology') terms them "monstrous changes."

elaborated this idea, and termed the minor variations "continuous" and the major "discontinuous." De Vries,* who followed Bateson, gave the name *fluctuations* to the slighter and more common changes, and termed the more abrupt or conspicuous *mutations*.

In addition to their degree there is, according to de Vries, another important difference between the two. He states that whereas fluctuation, or the tendency to fluctuate, is passed on from generation to generation, any specific fluctuation is not heritable. Mutations, on the other hand, are inherited.

Variations may be either progressive or regressive. "A progressive variation implies a complete recapitulation of the life history as presented by the parent, *plus* a prolongation, whereas a regressive variation implies an abbreviation of the life history, and therefore a reversion to the ancestral type."† Progressive variation is a positive process, and proceeds always by addition, whereas a regression is negative, for it takes place always by subtraction.

Examples of the Four Kinds of Variations.

- | | |
|--------------------------|-----------------------------|
| 1. Continuous, or minor. | 2. Discontinuous, or major. |
| (a) Progressive. | (a) Progressive. |
| (b) Regressive. | (b) Regressive. |

The differences between the two degrees of progressive variation may be exemplified by noting the relations of talent to genius.

The man of talent owes his ability to minor or *continuous* variation. Endowed with an unusual degree, say, of some artistic or intellectual faculty, he may either permit this ability to lie dormant, so that no one is the wiser or better for it, or he may choose, or fall into, a suitable environment, cultivating his talent until he becomes a Leighton, a Lawrence, a Kingsley or a Macdonald.

While the talented man owes his unusual ability to continuous variation the man of genius affords an instance of major or *discontinuous*‡ variation. Buffon has defined genius as an infinite capacity for taking pains. This, however, is exactly what it is *not*. No man by taking thought can become a genius, for the genius is invariably born, not made. Buffon himself, as well as Huxley, Tyndall, and

* Hugo de Vries, 'Species and Varieties, their Origin by Mutation.' De Vries maintains that mutations are not quantitatively but qualitatively different from fluctuations; but it is generally held that there is no specific difference between them, mutations being merely "the expression of an intenser degree of variation than fluctuations."

† Dr. Archdall Reid, 'The Principles of Heredity,' p. 361.

‡ Mr. Nisbet, in his book, 'The Insanity of Genius,' has pointed out that Professor Huxley was of the opinion that genius must be regarded as a "sport."

most of the celebrities of their day, were men of talent. But Byron, Burns, Coleridge, Darwin, and probably Pasteur and Herbert Spencer were geniuses, for their work was less the result of patient cultivation than of spontaneous impulse. Genius cannot be hid, but asserts itself in all but the most uncongenial environment. Thus, Shakespeare was a poor actor, living at a time when acting was a degraded and despised occupation. Yet, despite his poverty, his lack of education, the meanness of his surroundings, and the ignorance or even ignominy of his associates, he blazed out in the intellectual world like a meteor, throwing every other light into the shade. Nothing can be more striking than the contrast between his genius and the utter insignificance of his personal life. It is, indeed, so difficult to believe that a personality so commanding could have left no deeper impression upon his contemporaries that in order to avoid the Irish or one-horned dilemma a second horn has had to be invented, and we are told that the "Shakespeare" of the plays was not the uneducated actor of Stratford, a man who could not correctly write his own name, but some man of learning and exalted position, in all probability Francis Bacon.

A common example of *minor variation of the regressive kind* is the criminal, born of respectable parents. He begins with no natural aptitude towards crime. As a boy, perhaps, he atavistically lied or stole, and having been treated injudiciously, or sent to a bad school, the wrong tendencies by the influence of environment became permanent items of his character. In such cases as this either the predisposition to vice, or the education in vice, may not by itself be enough to determine the career, but the two acting together are sufficient permanently to turn the individual into wrong channels, to decide his character as a ne'er-do-weel, the skeleton in the cupboard of an otherwise moral family.

Major variations of similar kind on the other hand are very unusual. These constitute the black sheep of their flocks. They are sports or freaks of nature, for they owe none of their characteristics to their surroundings, or, at any rate, seem to act solely as the result of inborn tendencies, irrespective of environment. Criminals like Nero and Peter the Cruel are born criminals, and would indulge in crime under whatever circumstances they might be placed.

It is evident that variations of extreme degree, no matter of what kind, are essentially abnormal, and are often on or over the borderland between health and disease.

Let us now turn to some examples of variation furnished by the errors of growth and development.

A. Progressive Variation.

(a) *Minor*.—A good example of progressive variation is afforded by protracted old age. It is not likely that the normal life of a human being extends beyond the eightieth year. At any rate, there can be no doubt that octogenarians are exceptional. They must therefore be regarded as instances of variation in a minor degree, in part attributable to favourable surroundings, and in part to an inherent tendency to longevity. The variation is progressive because it protracts the duration of development and is therefore hyper-physiological in its tendency.

(b) *Major*.—Now and again, as a rare event, an individual passes his hundredth birthday. So rare, indeed, is this that centenarians become men of mark in their neighbourhood, and, like the Struldbrugs of Swift, are regarded by all as very exceptional people. There is reason to believe that the centenarian owes his extreme longevity, not to his habits nor to his surroundings, but to an inherent tendency to live an abnormally long life. We shall certainly be right in placing extreme longevity under the denomination of a mutation. It is an instance of progressive variation of extreme degree and shows strong hereditary tendencies.

B. Regressive Variation.

(a) *Minor*.—An instance of regressive variation of minor degree is furnished by the domestic cat. The coats of most cats are just as dark in winter as in summer, but if turned out of doors all the year round it will be noticed that in the coats of some cats the longer hairs become white at the tips so as to mitigate in some degree the blackness of the fur in which they are situated.

This is an instance of a latent variation of minor degree becoming patent in response to environment. It has chanced that among the many changes or fluctuations constantly taking place in the slighter characters one pertinent to the needs of the animal has come to the fore. It is therefore retained, and in course of time, if the need continue, would doubtless be increased. Variations of this kind, it is important to note, are not purposive, but appear by chance and are retained only if the environment be favourable. Up to a certain point, moreover, the longer any particular environment continues in action, the more intense and lasting is the variation. The truth of this statement is attested by the case of the arctic fox. This animal is naturally of a rufous or brownish colour, but variations have taken

place in the degree of pigmentation, and their presentation in response to its arctic environment has resulted in the snow-white coat. It must, however, be noted that this change is of the hair-pigment only, for the animal is not pink-eyed, and its nose remains black. Nevertheless, though the accumulated results of repeated variations are very conspicuous, the variation itself is not inherited; the offspring is not born white, and, if it grow up in a snowless country, its whiteness will in course of time cease to appear. The skin is plastic, and may respond to the stimulus of its surroundings in one of two ways, namely, by producing pigment or no pigment. But, in determining which of these two shall survive, the casting vote rests with the environment. The actual appearance of the variation is haphazard, but its persistence or non-persistence is purposive.

The albinism of the arctic fox is an instance of regressive variation of minor degree, continuons and suitable.

(b) **Major.**—Let us suppose, on the other hand, that amongst a litter of fox cubs, native to a country where arctic conditions do not exist, one is born devoid of pigment. This is a so-called “sport” or “freak of nature.” It is a regressive or negative condition, marking the absence of a quality, and hereditary; for if that particular cub, in course of time, be mated with another albino fox, and care be taken to keep up the process, a succession of albinos will result. It serves as an example of major or discontinuous variation.

Pathological Variation.

Under natural conditions, when no artificial breeding can take place, the perpetuation of any particular characteristic must depend upon its utility. If useful, or non-harmful, it may attract, or be attracted by, some similar individual of the opposite sex, and so will have a chance of being perpetuated. Or, if it mate with its opposite, the character will not, as we know from Mendelism, be lost; for though it may not appear in the individual, it will persist indefinitely in the sex-cells.

If it be a useful fluctuation it will continue only so long as it is in keeping with its surroundings. Two essentials are, therefore, required for the continuance of any characteristic. One is a minor variation, and the other is a suitable environment. The environment, it should be observed, never produces the variation but merely acts as its mordant, fixing it when it has proved a success.

Variations are not only physiological, but pathological. The

difference between these two states is not even one of degree, but of fitness. There is no line of division between degrees of variations of colour, of form, of size or of durability. Indeed, we are bound to include among variations all those anomalies of colour, form, and size, which constitute the pre-natal errors of development. Albinism belongs to the same group as the pigmented mole, the hare-lip and the club foot, which are all discontinuous variations, or "sports."

We have seen that development is a process co-eval with life, and that there is in nature no essential division of its anomalies into pre-natal and post-natal. Errors of development take place at all ages and are founded on similar grounds. Thus, all that array of diseases which we term the "presenile degenerations" must be regarded as variations, for they are just as much errors of development as are the malformations of pre-natal life. This is, indeed, foreshadowed by Bateson,* who says that "in problems of disease we meet again the same problem which we meet in variation, namely, changes which may be complete or specific, though occurring so suddenly as to exclude the hypothesis that selection has been the limiting cause." He explains that the diseases to which he refers are not due to specific organisms. They are, in fact, the diseases of intrinsic origin with which we are now dealing.

Among the degenerations or pathological variations taking place in the regressive periods of life we can detect two different classes or types, one of which corresponds with minor variations or fluctuations, and the other with the major variations or mutations of de Vries. We have, among the first, maladies like ordinary atrophic cirrhosis of the liver, granular kidney, general paralysis, tabes dorsalis. These are minor pathological variations, whose appearance is to a large extent determined by environment. For example, the persistent use of alcohol furnishes the environment of the liver-cells in atrophic cirrhosis. This stimulant-narcotic, bathing the cells day after day, for months or years at a stretch, constitutes just as much their environment as do snow and ice that of the arctic fox. It must be obvious, moreover, that the alcohol environment does not *produce* the senile variation called "cirrhosis," but only favours its appearance. A man may have been a drunkard for thirty years, and in the end his organs may be as free from all traces of presenility or senilism as if he had never taken a glass of alcoholic drink in his life. The chances are, however, that at least one organ possesses some latent tendency to presenile variation, and that this

* 'Materials for the Study of Variations,' p. 74.

will be made manifest by the alcohol environment, with the result that arterial fibrosis, chronic Bright's disease, general paralysis, cirrhosis of the liver, or some other degenerative disease, appears, according to the organ which happens to be most disposed to undergo this particular form of variation.

And it is obvious that alcohol is not the only form of cell environment likely to change latent disease variation into actual disease. Any agent, circumstance, or influence of a depressing nature may do the same.

Perhaps the best examples of the effect of different kinds of environment in producing each its appropriate morbid variation are furnished by the nervous system. We all recognise that dull, sad, monotonous surroundings tend to produce a lugubrious, depressed, ill-nourished condition of mind and body, and that out of this crystallise such diseases as melancholia and the different kinds of dementia. On the other hand, it is equally clear that an ill-regulated existence, too full of unhealthy excitement, leads to nervous instability, from which emanate such diseases as the insanities of adolescence, general paralysis, and the violent forms of madness. Much the same results may be produced by the "internal environment" consequent upon the presence of gout, syphilis, lead or alcohol. Diseases so produced are of the nature of continuous variations.

But there is another and more pronounced form of pathological variation which is, indeed, a major variation. Thus hypertrophic cirrhosis is of this nature, for it is not due to alcohol and originates from no other perceptible cause, but is discontinuous in its origin and heritable. It tends to occur at an earlier time of life than is usual with the atrophic form, and is usually met with during the progressive periods. So also is it with large white kidney, pseudo-hypertrophy of the brain, the giant hand, and those other anomalies of growth or development of the progressive periods of life, which are pronounced in degree, abrupt or spontaneous in origin, and occasionally inherited.

Although they may occur during the rising periods of development, they are, in reality, degenerative or regressive. The organ has lost the faculty of living to a normal period of life. It is, therefore, defective or regressive in the same way that skin, which has lost its pigment prematurely and spontaneously (albinism), is regressive.

Whatever may be said of the physiological distinctions between minor and major variations, they do not always remain distinct in their pathological aspects. Nothing seems clearer than that there is

no fundamental difference between the large white or the mottled kidney, the cause of which is unknown, and the small granular kidney due to gout or alcohol. We may call one a mutation and the other a fluctuation, but their pathological significance is identical. They are but different manifestations of the same disease process, with all sorts of gradations between them.

Much the same may be said of hypertrophic and atrophic cirrhosis of the liver. These are so graded that it is believed that they may, in certain cases, be no more than different stages of the same disease.

But in some other organs the difference between the two kinds of variation is so striking that they apparently have no connecting link. This is the case, for example, with some of the fibrous degenerations of the brain and of the spinal cord, where a wide separation exists between such major variations as Friedreich's disease and such minor variations as *tabes dorsalis*.

Though in mutations the variation is so abrupt that it seems to go off at a tangent from the usual track of ordinary development, it in reality runs along lines which have been already laid down. Thus, we are by no means surprised that an arctic animal should lose its colour, that a large proportion of the cats of a certain village should have six toes on each paw, or that a family of sheep should grow supernumerary auricles, but we are confident that a cow will never be born with a hand growing out of its head, or that a pig will have wings. So also is it with metaphysiological and pathological regressions. They, too, show their real character by keeping to biological precedents, and do not, like the bacteria and other extrinsic disease-producers, outrage Nature by taking up their abode where they have no right to be, or in other ways throwing its customs to the winds.

We must now ask wherein lies the similarity between such variation as the absence of pigment in the arctic fox, or of the albino fox, on the one hand, and those degenerative processes which we term cirrhosis of the liver or Bright's disease of the kidney on the other. So different are the consequences of these conditions that it seems absurd to class them together under the same heading. Nevertheless, when we consider this point it is soon evident that a similar principle may be at work in both cases, though leading to vastly different results.

For one thing, we can trace all stages between the purely physiological and the highly pathological. The distinctions between them are to be found in the degree to which the particular variation

harmonises with its normal surroundings. Thus the absence of pigment in the arctic fox is a physiological phenomenon. But when a fox, whose home is in a warm climate and among the rufous surroundings of the dead leaves of a forest, becomes white by means of major variation, the whiteness is glaringly out of keeping with the circumstances which form its setting. It renders the animal conspicuous, attracts the attention of the hounds, and gives warning to the animals upon which it preys. It is, therefore, not only abnormal, but to all intents and purposes a disease, for it leads, just as surely as do heart disease, goitre, or leprosy, to defective nutrition and an early death.

Let us now turn to that particular variation termed "chronic Bright's disease," and we shall see that the same may, in effect, be said of it also. Thus, an old man dies, say in his ninetieth year, apparently of sheer senility. He shows no sign of disease, no organ seems to be particularly at fault, and if, perchance, curiosity leads us to test his urine, it is possible that we may find nothing amiss. Yet, when he has passed peacefully away, should we examine his body, we should not be surprised to find that his organs have not all degenerated to the same extent. One or more may be even obviously in advance of the rest. Thus we shall, perhaps, find that his kidneys will present to the naked eye and to the microscope all the evidences of chronic Bright's disease. A case of this sort is, in fact, described later on. Now, to all intents and purposes, the kidneys were not diseased, for they apparently had nothing to do with shortening life. They were but little out of keeping with their surroundings. All the organs about them were also senile. Individual cells had almost finished their course, and the body, as a whole, was ripe for the sickle.

But a similar atrophic form of chronic Bright's disease, occurring to a similar degree in a man of forty, would give rise to such pronounced symptoms as would inevitably attract attention. The man would be desperately ill. We should not, indeed, expect to find his organs in such condition except at the termination of a long illness, and we should even then marvel that death had not taken place earlier. In short, the degree of disease exactly corresponds with the dissonance existing between the regressive organ and the rest of the body.

For this reason, the younger the patient the more deadly is any particular form of senilism which happens to be present, for the greater is the discrepancy between the regressive organ and its surroundings. Hence, in the body at large not only chronic Bright's

disease, but cancer, cirrhosis of the liver, sclerosis of arteries, leukaemia, general paralysis, and probably all other degenerative conditions are more rapid in their course and more fatal in young subjects than in the middle-aged or old; so that, generally speaking, the younger the patient the more violent the symptoms and the worse the prognosis.

Yet, strictly speaking, those who define disease as a lack of conformity with the surroundings are not always correct. It is a proper definition when applied to spontaneous disease, such as idiopathic cirrhosis of the liver, but not when applied to any disorder which has an extraneous cause or causes. Thus in the case of alcoholic cirrhosis the mischief is brought about, not by a discord between the liver and its circumstances, but on the contrary, by the very facility with which the liver has adapted itself to the morbid environment (alcohol) which has been forced upon it. It is the toxin, alcohol, which is primarily out of place, and not the fibrosis. So, also, a man affected with general infantilism—the result of the dirt, poor living, and other depressing surroundings of a London slum—is so far from being out of keeping with his circumstances that he owes his condition solely to the perfection with which he has accommodated himself to them.

The Origin of Variations.

The accumulated results of a long series of minor variations of the same nature, as exemplified in the arctic fox, seem to present very little difference from the mutation shown in the albino fox. Yet there is in practice a highly important difference between them, seeing that the first occurs as the result of environment, whereas the albinism seems to be independent of environment. If the arctic fox be transplanted to a temperate climate the winter variation would, in course of time, cease to exist, but albinism knows no such restrictions. In the one case only a tendency to whiteness is inherited; in the other it is the actual whiteness itself.

But in spite of these differences there is a connection between the two, which we shall best understand by inquiring into the causes of variation. It would be a great mistake to suppose that variation is inherent in all protoplasm. There is every reason to believe that it is no more than the impress which has been left upon cell life by the ebb and flow of the various influences which surround it. It is not the variation which is inherent, but the susceptibility to impressions.

Cyclical changes take place, not only from seasonal causes, but also as the result of the action and reaction of organisms upon each other. The Egyptian, Assyrian, Jewish, Greek, and Roman nations have had their birth, reached maturity, disseminated themselves over adjacent countries, and have had their decline and fall.

So also with races. They, too, follow the same rhythmic course of development and ultimately become extinct, handing on their better qualities to the younger races which spring up around them.

In short, it is evident that though development is largely influenced by environment, environment is not by itself sufficient to account for variation. Another factor is requisite, and this factor is to be found in periodicity or *rhythm*.

The law of rhythm is, indeed, so important and so universal in its application to development as to demand special attention. We therefore deal with it in a separate chapter. But before doing so it is necessary that something more should be said upon the subject of environment and its relations with variation.

Adaptation.

When we say that a variation is influenced by environment, we imply that the animal or plant is endowed with some faculty which enables it to be so impressed. This faculty, whereby the organism adjusts itself to its circumstances, is termed "adaptation."

Much difference of opinion exists as to the potency of adaptation in the production of species. Those who, like Bateson, are impressed with the enormous importance of variation, regard adaptation as a mere measure of expediency, and of very little consequence in the production of permanent characters. At the other extreme are Henslow and his followers, who claim for adaptation powers which are greater and more enduring than any variation, however pronounced. Midway between these comes Darwin himself, who believed that adaptation is on an equality with the lesser order of variations in the origination of species.

Under the name of *environment* we must include not only those influences which *surround* the animal and form its true circumstances, but also those which are taken into his interior, for though no longer the envelope of his body as a whole, they still constitute the environment of his cells.

The faculty of adaptation, whereby cells are suited to their immediate conditions, is in all likelihood of the same nature as that which constitutes intelligence in the brain-cells. We are probably right in

saying that the ordinary cells of a plant or animal possess a rudimentary intelligence, which enables them to make the requisite adjustments which occasion may call forth, and that this faculty becomes at last so perfect by cultivation and segregation as to account for all the swift and complex adjustments of which we are capable as reasoning beings. At the same time that these single cells are at work, the primitive adaptative faculty of early metazoic organisms comes into action, for each organ of the body seems to possess an adaptative power of its own, whereby it responds to influences which concern its work as a cell community. Hence, we recognise that adaptation in a human being is of a triple nature, for he is capable of making adjustments in his capacity as a complex individual; his organs carry on their work on a basis corresponding with their range of requirements; and the cells, constituting his tissues, are likewise capable of purposeful adjustments.

The relation of adaptation to variation is well shown in plants. Thus the beetroot which supplies Europe with so much of its sugar, can only be kept up to a point of commercial success by careful attention to the suitability of its surroundings, in respect of soil, temperature, rainfall, etc. Any relaxation of these efforts is speedily followed by a marked falling off in its sugar-bearing properties, leading to the failure of the crop. Evidently this is a case in which a particular character is more dependent upon adaptation than upon variation. On the other hand, it may be asked, how does it come to pass that a mimetic animal, such as a stick-insect, is not only adapted to its surroundings to an extraordinary degree of perfection, but retains its mimetic characters under all circumstances, as permanent indications of its species?

As a fact the characters produced by adaptation are never rendered specific by that process alone. The mordant which fixes them is variation. But difference of opinion exists as to whether the persistent adaptation actually produces the variation, or only fixes the variation when the latter chances to arrive. In all probability the relations of adaptation to variation are of both these characters. A chance variation, if of major degree, may at once persist if the environment be favourable.* But it is possible, though not yet proved, that an environment of long continuance may in time so act upon latent rhythms as practically to produce variation, though some other factor may be necessary actually to call it forth. Much the same thing, then, takes place as when a salt

* We are regarding sexual selection as an (highly important) item of the environment.

undergoes crystallisation. The first requirement is that the salt should be made into a solution of sufficient strength. Saturation once attained, all that is necessary is that the solution should receive some jar or shock. Definite or permanent crystals at once form out of the amorphous fluid. So in a similar way a suitable environment having, so to speak, saturated the adaptative capacities of the organism, a chance fertilisation by another organism equally saturated may furnish the shock required for the crystallisation of the adaptation into a definite and permanent form. Between temporary adaptation on the one hand, and its fixation by mutation on the other, the intermediate steps of fluctuation may play an important part in facilitating the change.*

If this be correct it will be seen that the relations between adaptation and variation are extremely flexible. In the case of some organisms, such as the stick-insect, long-continued adaptation seems to be by far the more important factor in the production of species; in other cases specific characters are probably more the result of variation.

The effect of environment in giving rise to anomalies of growth and development of the *whole body* is well exemplified in the production of dwarfism, infantilism, and senilism by insanitary slums. All must agree that paupers who live in over-crowded neighbourhoods, with all the evils implied in the phrase, are more stunted in growth and age sooner than do the rich who live in more spacious and salubrious quarters. Moreover, no one who has had experience of the disorder will, we think, deny that definite infantilism—at any rate that of a causal character—is more common among the poor people of the slums than it is elsewhere.

So also in the case of *organs* adaptation seems occasionally of more importance than variation. Thus the alcohol environment of the constant soaker produces its crop of infantilism and degeneration in the shape of amentia, dementia, liver cirrhosis, Bright's disease, and so forth, each of which is definitely a variation.

Lastly, the cancer of chimney-sweeps, and of the lips of the pipe-smoker, is a minor variation (senilism) of single *cells* invoked by the frequent irritating environment of soot, and of the clay pipe, respectively.

* This is Baldwin's view. The fluctuations mark time, as it were, until the requisite mutation turns up to perpetuate a change which has stood the test of prolonged use. (Comment by Professor Keeble.)

Rhythm.*

Few of us realise the enormous importance of periodicity or rhythm in evolution and individual development. We see that all organic beings respond to the stimulus of their surroundings, and that their progress or regress in the evolutionary scale is dependent upon the completeness with which they react to these extraneous impulses, good or evil. All protoplasm is endowed with this capacity, not only for receiving impressions, but for rendering them rhythmic, for storing them, and for giving them out. The object of this rhythmising property is manifest. If each stimulus called forth its one response and no more, the moulding of the plastic forms of life would be drawn out to an unthinkable length, and the earth would become cold and uninhabitable long before the evolution of its inhabitants is completed. By means of the rhythmic faculty the effect of each impulse is multiplied indefinitely. Rhythm secures economy of effort, so that one stimulus is made to serve the purpose of many.

Rhythm is, in fact, universal and essential, and is as important in the government of the details of the world, organic and inorganic, as in the scheme of the universe. The orderly sequence of solar and lunar changes, the undulations of sound, light, heat, electricity, and of less known radiations are all manifestations of rhythm. The rhythmic faculty, like all other primitive faculties, becomes more and more developed the higher we ascend the scale of life. Moreover, a special sense is gradually evolved whereby rhythm can be detected and appreciated, and this sense reaches its highest state in the most highly civilised. It is this sense which is jarred by harsh or unmusical sounds, by the clash of discordant colours, by irregularities of form, and by the monotonous, the ugly, and the bad wherever met with. It is this same sense which accounts for our delight in good music, good poetry, and the easily delivered, sonorous speech; for the pleasure with which we look upon the undulating landscape, the curved line, the arched bridge, and upon any well-balanced diversity of form or action.

Rhythm, no matter in what form it occurs, or by what name it is called, obeys certain rules or laws and is amenable to circumstances.

Thus an impulse may have to be repeated many times before its effects become periodic, or an occasional repetition may be all that is required; and synchronous responses of most vigorous character may even result from a single impulse. The original impulse may

* I am indebted to Professor Francis Darwin's Presidential Address at the British Association Meeting of 1908 for many of the ideas under this heading.

be momentary, as when a stone thrown into a pond gives rise to ripples, which continue to succeed one another long after the stone has reached the bottom. Or the impulse may be prolonged and continuous, as when a wind beats up a storm, producing waves which break on a shore a hundred miles or more from the seat of disturbance.

Lastly, the cadences produced by interrupted impulses may not be synchronous with them, as when irregular gusts of wind produce regular successions of waves.

Impulses which produce rhythmic effects upon development are either patent or latent, and for all practical purpose are of two kinds, to wit: (1) recurrent or seasonal, or (2) single, and either of intense degree, or prolonged or collective.

(1) **Recurrent or seasonal.**—These are impulses of frequent repetition and great regularity. They account for the daily alternations of work and sleep, for menstruation and for hybernation.

Rhythms of this type may continue long after the original impulse has ceased. Darwin, in his work on plant movements, gives some striking examples of the continuance of rhythmic movements in plants after the diurnal and nocturnal changes in which they originated were no longer in action.

An excellent example, quoted by Professor Francis Darwin from the work of Professor Keeble,* occurs in the case of the marine turbellarian worms *Convoluta Roscoffensis* investigated by the latter. These worms, which live in the sunshine, have entered into partnership with a unicellular plant (a green alga), and have done this so completely that the plant-cells within the worm have assumed the functions and importance of organs. Professor Keeble found that the worms undergo periodic up-and-down movements in keeping with the tides, and that these vertical movements still continue at the same intervals, though no longer purposive, after the removal of the worms to the stagnant water of an aquarium.

Many other examples might be mentioned of the continuance of similar habits in the higher members of the animal kingdom. Thus the habit of shedding the hair, a seasonal change in out-door animals, still goes on, in a slighter degree, when they become domesticated, though it is then no better than a nuisance. Traces of the habit are often to be detected in human beings; women especially are at times greatly concerned at the loss of handfuls of hair within the space of a few weeks, usually in the autumn, through no discernible cause. But the loss is usually temporary, for in most cases, after some months, the crop is as thick as ever.

* 'Plant-Animals' (Cambridge University Press).

Sometimes the cycle, once established, by change of circumstances is made to run counter to the impulse which set it going. Thus the black Australian swan, accustomed to lay its eggs at an appropriate season in Australia, when brought to Great Britain continues to lay them at the same time of the year, though the season is now inappropriate.

Rhythms of seasonal origin continue so long as they are required by circumstances, but when no longer pertinent, are prone gradually to cease. Thus, up to within recent evolutionary time the phases of the moon were of great social importance, but with the discovery of fire and subsequent improvements in artificial lighting, the need of moonshine for light-giving purpose has almost died out. Indications of the importance of moonshine are still to be observed in the rites and ceremonies of savage nations, in the restlessness of dogs on moonlight nights, and in similar disquiet among the insane which has led to their receiving the name of *lunatics*. When we hear the dog, man's companion from the beginning, baying the moon, or think of the old-time lunatic, chained, without candles, restless in the light poured into his cell at the full of the moon, it needs no effort to imagine their prehistoric forbears taking advantage of the treacherous light to go on expeditions of love, war, or chase. These cyclical lunar changes, though no longer of consequence in themselves, have apparently set going physiological rhythms, particularly in women, which continue to play a part in the economy of the reproductive apparatus.

(2) **Single or collective.**—Other cyclical changes are apparently due to irregular impulses of great importance and long continuance. These give rise to the so-called changes of life.

For example, the climacteric which affects both men and women between the ages of forty-five and fifty, rightly regarded as a time of peril to those who have been accustomed to neglect or abuse the rules of health, is in all likelihood due to the fact that this same period marked the termination of life in the highest animals for long ages of time.

There is some reason to believe that, in the course of the evolution of man from a more ape-like form, a period was at length reached during which the natural termination of life from senile decay took place between the ages of forty-five and fifty, or thereabout. Huxley says that the orang-outan probably lives to between forty and fifty years,* and the same is most likely true of other anthropoid apes.

* Essay 'On the Natural History of the Man-like Apes.'

De Quatrefages* writes of those primitive human beings, the Mincopies, that "the average duration of life is only about twenty-two years, and fifty is for them extreme old age." These estimates, as well as similar estimates of the age of Bosjesman and other negrito races, are evidently little better than conjectures. They indicate no more than that for an æon of time, during the early stone periods of human evolution, the normal length of life in all probability varied very little; whereas there is evidence that, during the historical period, especially the last hundred years, the natural duration of life has materially lengthened.

If we suppose that, for hundreds of thousands of years, men succumbed to senile decay between forty-five and fifty, and that, during the comparatively short space of a few thousand years, life was lengthened by another twenty to thirty years, then the cessation of female sexual life, the existence of a climacteric, and the especial tendency for premature senile changes to set in between forty-five and fifty are accounted for. If this age constitute a great and prolonged epoch in the phylogenetic development of man, it must also of necessity make a corresponding impress upon his ontogenetic development. When in the course of man's development he approaches this particular time of life, there will be a tendency for the old habit of mortality to assert itself. The even procession of life may even be checked for a space before it once more continues steadily on through the next stage. During these years, between forty-five and fifty, when the development of the human being moves slowly—doing obeisance, as it were, over the graves of his forefathers—he is peculiarly susceptible to adverse influence of a contemporary nature.

So also with other changes of life. They, too, are the rhythmic representation of deep-seated biologic phases, progressive or regressive.

Latent or subdued rhythms: Memory.—So far we have been concerned mainly with obvious rhythms; but rhythms, as we have seen, may settle down, becoming so subdued by lack of repetition of their original, or of some allied impulse, that we lose sight of them, though they still exist. The weaker the original impulse, and the less often the impulse is repeated, the sooner does the rhythm cease to be perceptible. But rhythms of great importance at the time of their first appearance may, no doubt, in course of time, become blurred so as to be half erased or even imperceptible, though still existing in a latent condition. But should appropriate circumstances

* 'Les Pygmées.'

arise the latent characteristic will be revealed, springing once more into activity, even after prolonged passivity.

Much the same process goes on, in fact, as when some long-forgotten event is remembered. When we say that we recall some impression to memory we mean that on some past occasion an event transpired which set going a series of automatic undulations in certain brain-cells. These undulations soon died down, or, in other words, ceased to affect consciousness, until stirred into activity by some appropriate stimulus, such as a repetition of the original incident, or of something akin to it. We think of memory as if it were solely a function of brain-cells. As a matter of fact, memory is one of the basic properties of all protoplasm, vegetable as well as animal, as much so as absorption or reproduction. In all cases the mechanism of memory remains fundamentally the same, though it becomes modified in detail. The stimulus applied to muscle does no more than awaken the memory of the cells, restarting rhythmic movements which have long remained in abeyance, and the germ-cell is but a cell endowed by cultivation with a prodigious memory. This memory, dating back to the beginning of life, is awakened by the stimulus of the contact of the complementary sperm-cell. These two, by the repetition of a primeval act, awaken a series of dormant rhythms which carry the fused cell, or zygote, through all the stages of its evolution. Memory of this kind runs in only the deeper grooves, lesser events being obliterated or forgotten.

Up to the time of birth the changes set going by the fusion of the germ- and sperm-cells seem to be purely automatic, but after birth the aid of *association* is called in to refresh memory and reinforce automatism. Contemporary events now act as reminders and play the part to which we are accustomed to refer under the terms of "environment" and "circumstances." The effect of environment is to bring out the lesser rhythms and to supply those fortuitous elements which cause post-natal human beings to differ so markedly from one another as compared with pre-natal. In other words, they tend to accentuate personality.

To return to our "variations." An act of racial memory is due to the repetition of a similar or correlated environment. Thus let us suppose that during the racial infancy of any particular man several generations of his ancestors passed through a period of depression, such as might be occasioned by subjugation, by slavery, poverty, famine, tending to affect them adversely, stunting their growth, retarding their development, ageing them prematurely. On the other hand, ensuing generations raised to prosperity by conquest,

riches or other causes of plenty, would tend to become strong and big, to mature late, and to live long. Such fluctuations as these might naturally leave impressions which would be repeated with more or less fidelity in the course of the progressive development of each succeeding unit.

But in the slow course of time the memory of these striking racial events would gradually become obscured or even obliterated. Nevertheless, the rhythm, once established, would never itself be abolished, but only its manifestations, so that when, in fulness of time, the man enters upon a period of adversity or of prosperity, and *this adversity or prosperity harmonises with the rhythm*, then the latent becomes patent and variation is established.

This variation would be of the *minor or continuous* order, for it would be the product of (a) a latent rhythm or "tendency," and (b) a more or less definite "cause."

To account for major or discontinuous variations we must repeat and extend what has already been said on the subject of racial memory.

Racial memory: Major or discontinuous variations.—The faculty of receiving, storing, and transmitting impressions produced by external objects, and of rendering them rhythmic or automatic, is inherent in all protoplasm. Like all such elemental properties, this property is possessed by some cells to a far higher degree than by others. Moreover, as with other properties, cells possessing this function highly intensified by cultivation are set apart from others into definite communities or organs. Of these organs there are two, the one being the brain and the other the sex organ, the one the seat of individual and the other of racial memory.

(1) In the brain certain cells receive impressions of current events, storing them, and rendering them rhythmic, in order that they may be reproduced if required. This process of reproduction is termed "memory," and the mechanism of memory is set into action by means of repetitions of the original impulse, or of correlated impulses.

(2) In the case of the sex organ the impressions received are not those of current events, but of the effect of current events upon the body. Thus the events which transpire during the life of a man plunged in a swamp of destitution are registered, not only in certain brain-cells, but to a lesser degree in every cell of his body, so that the structure of the whole man is modified by his depressing environment, rendering him meagre in size and prematurely old. This state of the body is itself committed to memory or registered by the

germ-plasm. But in this case the events of a whole life are compressed into such a compass as to constitute only one item of a memory extending back to the beginning of life. Hence no specific incident of a man's life is ever imparted to his offspring, and the inheritance of acquired characters is impossible.

Events which affect the racial memory through the medium of the body are destined to take one of two courses. If not repeated their rhythm gradually lessens, until it fades away and is forgotten beyond hope of recall. Or it may be renewed, either by repetition, or by the appearance of impressions of an allied character, which act mnemonically—that is, by correlation. The extent of the racial memory is dependent upon two sets of circumstances. The memory of the racial event may be perpetuated by the sheer force and extent of the original impression, as, for example, when long ages of senility setting in at fifty, or thereabout, produce the climacteric of the menopause. Or the event to be commemorated may be quite insignificant, and its magnification and transmission depend upon the frequency of its repetition, as in the seasonal changes of menstruation, sleep, hybernation, etc.

We see that racial memory, though its rhythms are latent in the sex-plasm, are also inherent in every organ and cell into which that sex-cell may eventually develop. Moreover, this racial memory behaves like individual memory, in that the more recent the impulse the clearer the memory, and the more readily evoked. Hence the remembrance of the human sex-cell of its early ancestry is confined to the barest outlines, whereas its remembrance of the change produced in recent stages of development is much more circumstantial.

In the series of memorising which constitutes development the first impulse takes place when the cell of the one sex meets the cell of the other sex. This at once furnishes the clue to the next step, much as the brain recalls a forgotten incident by rehearsing the events by which it was preceded. So, in a similar way, the development of the animal proceeds, link by link, each link being forged on to the one before it. By successive waves of correlation of this sort, rattled off one after the other, development rapidly advances from precedent to precedent, until it arrives at the great climacteric of birth, when the last stage of pre-human evolution is left behind, and the anthropoid ape merges into the man.

Up to this time only the great elemental events of evolution have been remembered, but now, as the rehearsal proceeds, and new waves surge up, lesser events are recalled; and the nearer we approach the precincts of historical times the more copious does the

memory become, until at last the effects of historical, or, possibly, even family events are recollected.

Major variations, biological and pathological.—The racial, like the individual memory, is not infallible. As we have just seen, minor events are soon forgotten, and, in course of time, events of great importance at the period of their occurrence sink gradually into oblivion. But now and again, as a rarity, there is a lapse of memory, in which some highly important stage of development is omitted.

This forgetfulness may, for example, occur in the act of palate building, during the first months of fetal life, with the result that the whole process of bodily construction is marred by the presence of a cleft in an important part of the alimentary canal. The lapse of memory may be confined to this one particular detail, or the forgetfulness may be of more than one part, so that not only is there a cleft palate, but a hare-lip, or a slit extending from the mouth to the ear. In such cases as this the lapse of memory may be partly the outcome of failure of correlation, whereby the act of building the palate having lapsed, an important clue is missing, with the result that other acts of construction are also forgotten.

Such mistakes of racial memory may occur at any stage in the development of the human being, and account for all mutations of a regressive character. Albinism, infantilism of the kidney, liver, brain, and other organs, renal and other rests, and general idiopathic infantilism are all to be explained in this way; and probably, whenever senilism occurs as a major variation, it is due to an act of racial forgetfulness. When we see a kidney or liver break down prematurely, degenerating into the fibrous organ of chronic Bright's disease, or of cirrhosis respectively, we may consider that there was a prior infantilism, or, at any rate, a defect in the process of racial memory, whereby the degeneration of old age came about prematurely.

Major progressive variations.—Ordinary brain memory is an exceedingly variable process, some impressions being remembered far more vividly than others, without any correspondence in their importance.

So also the memory of some historical events of minor significance has been handed down with a wealth of detail entirely lacking in events not far removed from them in point of time, and of much greater importance. Thus we know far more of the circumstances connected with the murder of Thomas à Becket than we do of those in connection with the great constitutional changes which took place

in the same reign. Whereas Becket's murder has become one of the most widely known events of English history, who is there that knows anything of the constitutions of Clarendon, and of the Assizes of Clarendon and Northampton? Yet Becket's death was in reality of quite minor significance compared with the latter, which constitute the foundation of our modern legal procedure. The murder was, in fact, little more than an incident occurring in the course of a tremendous legal reform. Yet, were it not for the written records, the latter would by this time have been almost forgotten, whereas the by-product has left an indelible impression upon the national memory.

So also is it with racial memory, the events remembered are not always of an importance commensurate with the position they originally occupied, and now and then they obtrude to such an extraordinary extent as to become abnormal. In some individuals, moreover, the racial memory is so erratic that, while certain important events are unduly prominent, others are forgotten. It is in this fashion that progressive and regressive variations take place in the same individual, giving rise to that inequality which characterises the development of so-called degenerates. Thus one and the same man may have a hare-lip, or a club-foot, and yet be a genius. Or his lack of developmental balance may show itself in the possession of a giant hand and a microcephalic brain, or as obesity in one member of a family and pernicious anæmia or chronic Bright's disease in another.

Methods of destroying or increasing the rhythms of racial memory.—It is possible directly to tamper with the germ-plasm and thereby derange its faculty of transmitting impressions. Thus we have seen that syphilis, lead, and alcohol is each capable of producing deformities by its direct action upon the germ or fœtus. Similar effects have been wrought upon lower animals by mechanical interference. These methods are comparable with the destruction of memory which may result when the brain is damaged by concussion or other injury.

So also rhythms may be annulled or heightened by the *effects of sexual selection*, or the blending of qualities which is brought about by mating. Sexual selection is often regarded too much from the standpoint of the advantages to be gained thereby. It makes, no doubt, for the good of the race in the long run, but it must not be forgotten that undesirable as well as desirable qualities are thereby accentuated. Let us suppose that two individuals are married, both of whom happen to possess, in a latent condition, rhythmic impres-

sions of bygone racial disasters in a state ripe for expression. If no marriage had taken place each of these latent troubles might never have affected the racial consciousness, or, if revealed by some suitable environment, would have occurred only in a minor form, not sufficiently severe to affect the germ-plasm. But the act of mating, by doubling the undulations, has the effect of a violent awakening. Just as a match rubbed on the rough surface of a match-box bursts into flames, so the dormant impulses of bygone generations are suddenly roused into activity. The latent becomes revealed in a high degree of intensity, and a variation results. So violent may the renewed impulse be that a fresh series of vibrations is started and handed down to posterity as an hereditary character.

Hence, in the production of a major variation, it is not essential that the original stimulus should have been of great intensity or of long duration. There may conceivably be means of accentuating latent impulses. A celebrated engineer used to say that three men starting vibrations on the Forth Bridge could break it down, provided they could time each succeeding vibration so as exactly to synchronise with the one before it. So also it is possible that a comparatively slight rhythm, once started, might, by the chance working of succeeding rhythms of a similar order, be magnified into an impulse of considerable intensity.

Lesser rhythms.—Evidently the classification of rhythms just given is inadequate, for we have only referred to those which are produced by impressions of great intensity. It must be obvious that there are lesser impressions and lesser rhythms, and that though singly these may be of hardly any consequence, yet collectively they may exert an important influence upon our lives.

Some of them are seasonal, others erratic. Thus close observation has shown that men as well as women are liable to mensal fluctuations. These fluctuations are far more readily to be detected in some men than in others. They are, of course, less regular in men than in women; and, no doubt, the absence of the machine-like regularity has prevented their being generally recognised. They account for some of the off-days, as well as for times of well-being and buoyancy, to which most men are liable, which cannot otherwise be explained. Moods are prone to ebb and flow, the elation of one time being followed by the depression of another. Few writers, musicians, actors, tennis-players, can keep to the same level of excellence. Most are conscious of an occasional slackening or reinforcement of power, quite apart from food or drink, cloud or

sunshine, or any other circumstance. In some the mysterious changes of moods are so pronounced as to dominate their whole output of work; so that the author, say, cannot for a period write a single page to his satisfaction, and is perhaps obliged to throw up all attempts until the spirit moves him, and then the flow of ideas may be so copious as abundantly to make up for the previous drought.

Fluctuations of this sort have an important bearing upon health, for the man under the influence of a depressing rhythm is, in all likelihood, more vulnerable to the assaults of extrinsic disease than when he is rising on a wave of atavistic prosperity. This is probably the explanation of the fact that a child exposed to infection from some microbial disease will be immune at one time and not at another; that under almost identical circumstances a man one day falls a victim to asthma or to migraine, and on another day "never felt better in his life."

But what is of more consequence is to distinguish between the rhythms which originate during the life of the individual and those which are derived from his pre-existing ancestors. This separation of reversionary from contemporary rhythms is so important and is so closely bound up with heredity that it is best left to be dealt with just before we enter upon that subject.

Rhythms of contemporary origin go by the name of habit, memory, custom. Examples of rhythms pertinent to our subject are afforded by alcohol and other narcotics. Liability to over-indulgence in alcohol is partly the outcome of inherent susceptibility and partly of the weakness of inhibitory factors. Under ordinary circumstances the cells of the body soon acquire the habit of making a periodical and daily demand for some form of alcoholic liquor. This, as a rule, is not very insistent, so that the rhythm or habit is easily broken. But increase of the stimulus or of the susceptibility, or diminution of control due to illness, shock, or some other circumstance, may result in a rhythm of far greater intensity. The drinker may even become a *victim* to his rhythm, so that its satisfaction becomes imperative, brutally demanding satisfaction in spite of the obvious and cruel damage which is being done to the tissues. Sometimes the susceptibility to the alcohol rhythm is so great that a very few repetitions of the stimulus are sufficient to establish a daily, weekly, quarterly or more erratic periodicity. The victim may at the outset, or for an interval, have very little desire for alcohol, and then suddenly and without cause be seized with an uncontrollable impulse to drink to excess. This drinking bout,

after lasting a few days, will then spontaneously terminate in depression and remorse, accompanied by vows of amendment which may even last until they are silenced for a time by the re-appearance of the rhythm.

Rhythms of a similar nature, and termed "habits," account for some cases of depravity, and even of insanity. Thoughts of revenge, of libidity, of remorse or of religious despondency by repetition become more or less permanent, and may, indeed, be accentuated up to the point of disease, ending perhaps in suicide or murder.

It is by no means certain that habits or rhythms are ever the result of acquisition alone, at all events they must in most cases be partly inborn; and, as a rule, it is well-nigh impossible to say to what extent they are acquired, and to what extent they are of germinal origin.

Disorders of rhythm.—Rhythm seems to be liable to irregularities and to excess or defect, like every other faculty or quality. Certain maladies cannot be classified under the head of growth or development or nutrition. Among these are epilepsy, migraine, spermatorrhœa, and fever. These seem to be disorders of the apparatus of rhythm. Epilepsy is a periodical and excessive discharge of rhythmic motor impulses. It may be either spontaneous (epilepsy) or the result of a toxin (eclampsia). In migraine and in tic douloureux the impulses are sensory. Spermatorrhœa is a local epilepsy of the reproductive mechanism. In rabies or strychnine poisoning the muscle-nerve combination is thrown into paroxysms of uncontrollable rhythmic activity by the action of a toxin. Another rhythm liable to morbid extremes is the heat rhythm. Under certain conditions the usual morning ebb and evening flow become exaggerated. Many toxins have a selective affinity for this rhythm, and so give rise to fever. But occasionally, as a rare event, the caloric rhythm is intensified for weeks or months together though no cause can be found. Cases of this sort are remarkable for the absence of other symptoms suggestive of intoxication and seem to be due solely to derangement of the periodical supply of heat.

Heredity.

The conclusions at which we have so far arrived may be embodied in four propositions:

All organised beings are plastic to their environment.

Impressions produced by environment are liable to become rhythmic.

Rhythms are facilitated by the repetition of either the like or of similar (associated) impressions.

Rhythms are either the result of impressions which were in action in bygone ages, and are stored in the germ-plasm, or of contemporary impressions.

Our object is now to show the relation between impressions or rhythms of contemporary origin and those of reversionary origin.

It is almost regarded as one of the axioms of biology that no acquired character is inherited. It must be equally self-evident that no acquisition is ever lost. Every circumstance which is brought to bear upon the individual must leave its mark, however infinitesimal, upon him, assisting in some measure to shape his destiny, and its shadow or echo will, in all probability, also be recorded upon the sensitised plate of his germ-plasm. This germinal record, intensified or minified by subsequent events, may subsequently be handed down as an heir-loom to succeeding generations in order that its writings may be intensified or blurred, or fresh writings stamped upon it.

A good example of the supposed inheritance of an acquired disease is furnished by alcohol. When the father and several members of his family are drunkards, it is usually said the children inherit their drinking habits from the father. They do no such thing. What they inherit is a tendency easily to succumb to alcohol, or, as we have seen, to fall readily into the drinking rhythm. It is the periodicity which is transmitted, not the liking for alcohol. So also tubercle, lead, and syphilis are prone to affect certain families far more severely than others. This, of course, does not mean that the disease is inherited, but that the defective immunity is inherited, or that the environment is highly conducive to the acquisition of drinking habits.

No parent, however good or however bad, has ever handed down his good or bad qualities to his children. All that he can do is to transmit a germ-plasm containing *potentialities* for good or evil, such as he himself already received from his ancestors. He may directly poison his child with syphilis, with alcohol, or with lead, but he cannot be held responsible for the transmission of truly hereditary diseases, except in so far as he deliberately marries into a family known to possess disease, or undesirable tendencies which may eventuate in disease. His ability to damage his children is confined to the one highly important particular of providing them with a pernicious environment, but in all probability only his remote descendants will be affected by the extremely slight deepening of

undesirable grooves affected by him during the days prior to the conception of offspring. As the son recapitulates the stages of his development, whatever minute contribution to character he may derive from his father will not come to the surface until the influence of all previous ancestral experiences has been exhausted.

While it is true that no acquired character can be transmitted, it must not be forgotten that it is quite possible adversely to affect the germ-plasm through the instrumentality of toxins. These seem to go direct to the germinal cells, and to the gamete itself, acting with all the force of a bad ancestry. As we have already seen, the toxins, which are, above all, capable of producing these disastrous results, are those of wine (alcohol) and syphilis, as well as lead, and probably tubercle. But though capable of warping the whole existence of the individual, there is no evidence that their influence extends beyond him to his descendants.

Mendelism.*

Six years after Darwin had published his work on the 'Origin of Species,' Gregor Mendel, an Austrian monk, read a paper at a meeting of the Natural History Society of Brunn, on the subject of "Experiments in Plant Hybridisation." This paper, which was for a time buried in the pages of the Society's proceedings, was disinterred thirty-five years later, after the death of Mendel, by the Dutch botanist, Hugo de Vries. Mendel's paper was found to be of epoch-making importance. Before his time heredity was regarded as a highly speculative subject, so that no one ventured to predict what exactly would happen when plants or animals were mated together. Mendel, by his one pamphlet, suddenly, as by the act of an enchanter, reduced this chaos into order. Where there had before seemed to be no more than the working of blind chance, is now seen, thanks to Mendel, a matter of mathematical formulæ. A more sudden and complete transformation can hardly be imagined.

In lieu of attempting to follow the course of the assemblage of characters which make up the individual, Mendel determined to investigate the inheritance of individual unit characters. Working with plants, it was easy for him to choose races, *e.g.*, of peas, which differed from one another by a single character, such as tallness as

* See 'Mendel's Principles of Heredity,' by Professor Bateson. An excellent short account is also to be found in the 'Gardener's Chronicle' of July 24th, 1909, and in 'Mendelism,' by Mr. R. L. Punnett. We are also greatly indebted to Professor Keeble for most of this section.

opposed to shortness, roundness of seeds as opposed to wrinkling. Selecting plants which differed from one another by one single character, he observed that one character appeared in the offspring (F_1 = 1st filial generation) apparently to the exclusion of the other. For example, F_1 of a cross between the tall and short peas were tall, and hence he called this character "dominant," and the suppressed character "recessive." On selfing (self-fertilising) F_1 plants, he found that, of the offspring in the resulting generation (F_2), on an average three were tall and one short. This phenomenon of the reappearance of the recessive of the original pair of characters (in this case, dwarfness), side by side with the other character (tallness) of the parents Mendel terms "segregation." By subsequent selfing of these tall and dwarf plants he showed that the recessive dwarf breeds true to dwarfism, and of the three tall, one breeds true to that character, and is pure with respect to tallness, while the other two behave like the peas of the F_1 generation, and give rise each to offspring of which three are tall and one dwarf.

To account for these remarkable phenomena Mendel put forward the hypothesis of gametic purity. In this hypothesis the sex-cells (gametes) carry one character, and one character only. Recent work by Bateson and his pupils and others has confirmed Mendel's experimental results, and rendered it probable that the dominant character is a *presence* character—in other words it is due to some definite thing carried in the germ-cells; and the recessive character is due to the *absence* of that which causes the dominant character. For example, tallness is due to the presence of something in the gametes, dwarfness to its absence. The theory of gametic purity may be stated in terms of this "presence and absence hypothesis." Thus a gamete is a single cell which may carry the character, or it may not. It cannot both carry it and not carry it. The individual (zygote), on the other hand, is formed by the fusion of two gametes (male and female). Hence it is a dual structure. By reason of its dual nature it may derive the same character from each parent (*e. g.* tallness) or the opposite of this character (dwarfness); or it may derive tallness from one of the gametes which formed it, and dwarfness from the other.

In the two former cases it is pure (homozygous), in the first case for tallness, in the second, for dwarfness. In the last case it is impure (heterozygous) with respect to tallness.

Expressing the idea in simple symbols, let—

T = tallness factor;

t = dwarfness (*i. e.* not tall) factor;

The pure tall parent = T T producing only T, T, T, T gametes ;
the pure dwarf parent = t t producing only t, t, t, t gametes.

In the cross between tall and dwarf T gamete meets t gamete,
producing an F₁ zygote T t ; and T being dominant, the zygote of
F₁ appears tall.

The F₁ plants (T t) produce gametes $\frac{T\ T\ T\ T\ T}{t\ t\ t\ t\ t}$ in vast numbers.

These gametes mate by chance, and hence in every four cases we
have—

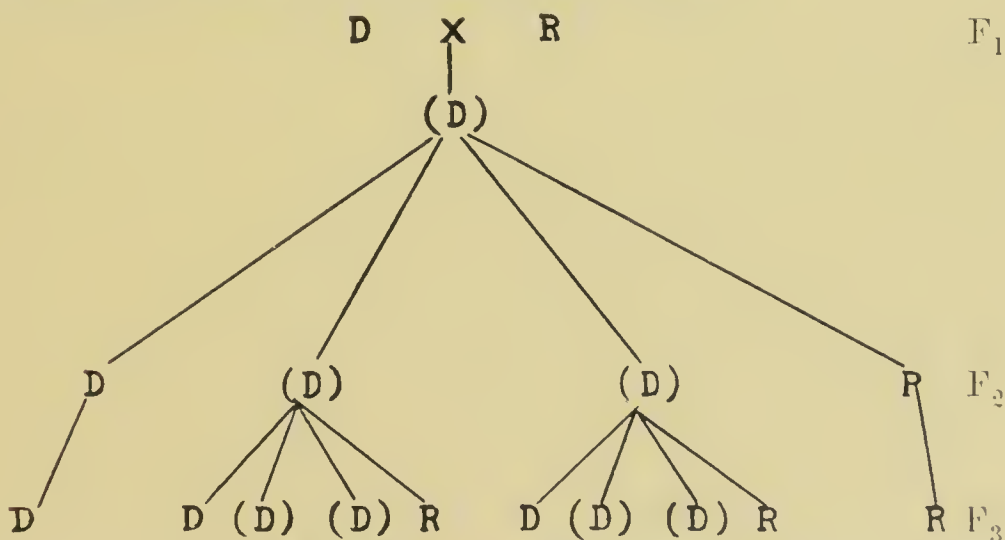
	T	t	male gametes
female T	T T	T t	
gametes t	T t	t t	

i. e. 1 T T ; 2 T t ; 1 t t.*

T T being indistinguishable from T t (both being tall), we get 3
tall, 1 dwarf.

Subsequent breeding proves that of the three tall, one is pure
(T T) to the character of tallness, and two are impure. The latter
selfed give rise, like the F₁ plants, on the average to three tall and
one dwarf.

* These relations are set forth in the following scheme where the R stands for the
recessive and D for the dominant character. The impure dominants are distinguished
by being placed in brackets. When self fertilised each continues to produce domi-
nants and recessives in the proportion of one pure dominant, two impure dominants,
and one recessive, no matter in what generation it is placed.



From 'Mendelism,' R. C. Punnett.

If instead of one character, two independent characters are involved, F_1 will show both dominant characters and F_2 will contain individuals of four types, viz. (1) those resembling F_1 , (2) those exhibiting one dominant character only, (3) those exhibiting the other dominant character, and (4) those which show the two recessive characters. For example, if tall round and dwarf wrinkled peas are crossed with one another, F_1 = tall round, and F_2 = tall round, tall wrinkled, dwarf round and dwarf wrinkled, the ratios being—2 : 3 : 3 : 1.

This is Mendelism in its simplest form, and the alphabet of the new science of heredity. Like all sciences, it is requisite that it should have a terminology of its own. In Mendelian language the pair of segregating unit characters (the dominant and the recessive) is termed an allelomorphic pair. The union of gametes bearing single characters is termed *monhybridism*, that of two characters *dihybridism*.

It can readily be conjectured that we have here the elements of great complexity. Their bearings upon our particular subject may be summed up as follows :

(1) A character which is recessive will be missing in the first generation, but will appear in the second.

(2) A character is not necessarily non-transmissible when it does not appear for many generations, for it may be only latent, eventually to turn up long after its first appearance has been forgotten.

Mendelism also provides satisfactory explanation for the occurrence of (3) reversions, and (4) sterility, and other problems of heredity met with in disease.

So far, work on this subject of Mendelism has been done mainly on plants. Plant material is so common, so easy to experiment with, and the products of mating are so copious, that the principles can be worked out far more easily in plants than in animals. These difficulties are multiplied many times when the gamete we have to deal with is not that of a pea, but of a man. In man we are at once embarrassed by the multiplicity of characters, not one of which stands out from the others so conspicuously as the colour of the petals of a sweet pea stands out from pea characters. For this reason researches which have hitherto been made upon human characters have been restricted chiefly to such monstrosities as the claw hand, polydactylism, albinism, hæmophilia, though it is true that the genetics of brown (dominant) and blue (recessive) eyes have also received attention. These observations show that Mendelian principles apply to man as well as to peas. In short there is every reason to believe that heredity invariably follows

Mendelian laws. Mendelism cannot in the present state of our knowledge be applied in a large number of pathological mutations, for many reasons. Thus its application to acardiac or brainless monsters is out of the question, seeing that the mutation is incompatible with life. Other variations, like that of microcephalism, cryptorchism, cretinism, are associated with such defects of the reproductive apparatus as must effectually prevent their transmission. Yet others, such as obesity, general infantilism, genius, are so often accompanied by correlated partial or complete sterility that very little can be gathered as to their Mendelian characters.

In this connection a point of great importance in its bearing on our subject may now be taken into consideration. It may be objected that extremes of growth or of development are not proved to be mutations (major variations) unless they can be shown to have been transmitted. But if the variation be associated with a sterilising disorder of the reproductive organs, the laws of heredity, though applicable, are not, in the present state of our knowledge, to be depended upon. And it is not requisite that there should be actual sterility, for a mere approach to sterility, such as may limit, and not stop, the production of offspring, may be quite enough to derange the results. In all probability the Mendelian law only applies when there is some approximate equality in the reproductive powers of the parents; so that when that approximate equality no longer exists, it is by no means unlikely that the transmission of the variation will either be very irregular or will not take place.

For these and other reasons we cannot regard evidence of hereditary transmission as essential to the constitution of a major variation of growth or development. The heredity occurs, but may be so obscured that it does not come to the surface. Of far greater import are the complete absence of an environment capable of setting up the variation, and the occurrence of the variation in a very marked form, or in a young subject. At the same time, *when there is definite evidence of heredity that evidence is conclusive, stamping the nature of the variation beyond question.*

Transforming heredity.—It has been noticed that when a heritable deformity occurs in a family it may alternate with another heritable disorder. Thus hereditary epilepsy has been known to occur in members of a family of which other members are subject to persistent hereditary œdema of the legs.*

In other cases the heredity is more irregular, so that a family characterised by the occurrence of, say, cleft palate among its

* Drs. Hope and French, 'Quarterly Journal of Medicine,' 1908, p. 347.

members may be distinguished by the occasional appearance of other malformations.

This transforming heredity is sometimes due to variations being dominant in the one sex and recessive in the other. Thus hæmophilia dominates in the male and albinism in the female, and cases have been recorded in which they have appeared in different members of the same family. In other cases it is possible that the variation which appears first may be recessive, and some secondary (correlated) variation dominant. In that event the original variation will apparently undergo transformation to variation of another sort in the course of transmission. It is probably in some such way as this that the problem of familial correlation of diseases (*i. e.* the occurrence of degeneration or growth disorders in different forms among different members of the same family) will be solved.

XI

SUMMARY; CONCLUSIONS

EVERYTHING that is known on the subject of disease points to the conclusion that it is not a *lusus naturæ*, but is, generally speaking, a natural or preternatural process. Pathology, in fact, is not a sharply defined department of science cut off from all other departments by the taint of morbidity, but is as much a constituent of biology as are natural history, botany, ethnology, or, indeed, physiology itself. This is shown both by an examination of the agencies which provoke disease from without and of those which are responsible for the origination of disease from within.

The origin and history of any disease of the human body caused by the invasion of living organisms must be largely influenced by succeeding phases in the life cycle of its microphyte. The infectious fevers are endemic, have an incubation period, a period of invasion, a period of decline, and the occurrence of one attack acts as a protection against another. One or more of these characters may be absent, or but slightly marked in any particular case, yet they occur sufficiently often to be distinctive of this class of disease. The diseases have a biological basis, for they are founded upon certain characters and stages in the natural history of the bacteria which produce them, and of the cells they attack.

So, in the same way, the group characters of the diseases with which we are now concerned, though not all present in unmistakable form in every instance, yet occur sufficiently often to give character to the class. Moreover, they have a biological foundation, but this is to be found in the tissues themselves, and not in any outside source. In the bacterial diseases we have to do with an invasion, and a study of the group symptoms is a study of the methods of the invader and of the battles that ensue. But in these other diseases we are concerned with a revolution or a rebellion. The disorder is primarily intrinsic, though it may be fostered by outside help, and shows itself in an exaggeration of certain normal phases in the life-history of the cells or organs involved.

It will be evident that any disease which is nothing more than excess or defect of growth will not only have its foundation in natural growth, but will show traces of the original pattern throughout the whole of its course. And the same may be said in effect of morbid defect, or immaturity, and excess, or prematurity of development. There is no abrogation of natural processes. In every case the "symptoms" are the result of natural events minified or exaggerated. The group characters of growth and developmental diseases can only be understood by keeping this fact clearly in view. There is no spreading from one body to another, for such an occurrence would imply an attack from outside. The developmental diseases are not infectious. Those of cells and organs are local diseases, as distinguished from many bacterial diseases, which directly affect all parts of the body by the circulation of their toxins. They are, moreover, the outcome of variation. It is true that the variation is of morbid degree, but it is, none the less, a variation, and liable to be affected by the laws which govern variation. These diseases are, moreover, sporadic and sometimes hereditary.

Let us now take each form of disease of the endogenetic group in turn and see how its characters are determined by natural antecedents.

The innocent tumours and simple hyperplasia of organs.—The former are simple overgrowths of the tissues from which they spring. They are altered, it is true, by some disorder in the arrangement of the cells, owing partly to the way in which they crowd one another, as if eager to escape from the trammels of physiological restraint. They are overgrowths mixed with a mild degree of consecutive degeneration. Similarly it is patent that the hyperplasias of organs, such as the goitre of Graves's disease and the enlarged muscles of the "strong man," are nothing more than excesses of growth. The reason why excesses of growth of cells are more exuberant and disorderly than the excesses of growth of organs is readily understood when they are examined from the biological standpoint. Cells are, as we have seen, the primitive units of animal life, representing as they do the unicellular protozoa. They are to the scheme of development of the individual animal what the amoeba is to the scheme of evolution of the animal kingdom. It is, therefore, only to be expected that they should behave in an unruly way when they recover a large measure of independence. On the other hand, the organs, corresponding as they do with the first compound animal or primitive organism, have as their prototype a structure of more advanced and more orderly stage of development.

The assemblage of cells together for mutual benefit in an organ creates a tie between the various units which is maintained in disease. Hence an overgrowth of cell units, such as those of fat, in the form of an innocent tumour (lipoma), or of thyroid cells in thyroid adenomata, is far more disorderly, and, as a rule, more pronounced than when an entire organ, such as the thyroid gland, is affected with a similar overgrowth (parenchymatous goitre).

The degenerations of cells and organs.—In the cancers, and in organs affected with fibrosis or cellular degeneration, single cells in the one case, and entire organs in the other, have evidently undergone some degrading process to a far greater extent than is the case with the excesses of *growth* of the same units. They are all true malformations or deformities and something more. But here again we must be careful to draw a line between cells and organs. The return of the organised *cell* to its primitive state must necessarily be accompanied with far worse results than the return of an *organ* to its corresponding simplicity. Malignant tumours are collections of cells which have thrown over nearly every vestige of restraint, not of growth only, but of development as well. Their constituent cells are radically altered, both in quantity and quality. There is just as wide a separation between a primary cancer, say of the liver, and cirrhosis of that organ, as there is between an amoeba and a sponge. The cancer-cell, like its unicellular prototype, is capable of almost any degree of unrestrained licence, but the degenerated organ never retrogrades, as a whole, to cellular independence. It always remains a compact mass of cells strung together on a more or less perfect intra-cellular framework, and the cells invariably maintain some degree of mutual dependence.

Hence, there is this difference between primary (malignant) degeneration of cells and primary degeneration of organs, in that the former have reached the limits of their retrogression, whereas in the latter the cells have only arrived at a half-way stage, and are individually still capable of further degradation. But having arrived at this half-way stage, they are more likely to complete their journey than are the cells of the normal organ. It is for this reason that cirrhosis of the liver, fibrous goitre, ichthyosis of the tongue, osteomalacia, osteitis deformans, and other of the degenerations are prone to become the seat of cancer. An instructive instance of the stages in this road to ruin is furnished by a lymph-gland. The normal lymph-gland has a fairly definite structure. There is a certain ratio between its cortex and its medulla and the amount of its fibrous trabeculae. But in the

degenerated gland of Hodgkin's disease no such division can be detected, or, at any rate, it becomes much less distinct. The structure of the gland is simplified or degraded. This simplification is not the only expression of degradation, for the same fact is indicated by proliferation. The degenerated gland is a bigger gland. But let further (cell) degeneration set in, and a still more marked change is noted. The cells which were confined within the capsule of the amplified organ again proliferate to a far greater degree; they become aggressive, burst through the capsule and invade the surrounding tissue. The cell has reached the limits of its degeneration, and has become a unit of a lymphosarcoma. So also in cirrhosis of the liver, the tendency is to reduce all the different cells to cells of one kind. But such simplified cells never break the bounds of the organ itself. In order to do so, further (unicellular) degeneration must ensue, and when that happens, mushroom-like growths push up and burst through the capsule and send offshoots to adjacent parts of the body.

In dealing with the pathology of the degenerations of cells and organs it is necessary to keep closely in view the physiological processes which lie at their root. By so doing it will be evident that all the various phases of normal development, which were mentioned in the chapter on that subject, are represented in these abnormal excesses. These may now be referred to under similar headings.

Thus *diversity* in the characters of the different forms of cancer and of the degenerations of organs is entirely due to the great variety of cells and tissues which go to make up the structure of organs. In fine, each sort of cell is liable to stamp its individuality on its corresponding cancer, and each tissue of an organ may be the starting-point, and give the tone to a degeneration. Hence, every tissue and every organ is vulnerable to degeneration from any one of its normal aspects. The sarcomata are the cancers of the connective tissues, the carcinomata of the epithelial. The cylindroma proceeds from malignant degeneration of the large intestines; while epithelioma of the lip differs from that of the rectum, just as the normal epithelium of the one part differs from the normal epithelium of the other. So also bone-marrow may be attacked from each of its three physiological aspects. It suffers as a red-blood-making organ in pernicious anæmia; as a white-blood-making organ in leucæmia; and as a bone derivative in osteomalacia. Each of these different diseases differs in its symptoms and anatomy from the others. In each case the particular function and structure affected is caricatured and distorted.

Another physiological factor of great importance in producing variation is *age*. This is so evident that little need be said on this score.

The sarcomata occur during the whole period of development, and the carcinomata during the retrogressive half. The cancers of early life tend to run a rapid course, because the processes of development then move quickly. For the same reason cancer attacking the breast during lactation is, as a rule, more rapid in its course than when the gland is normally at rest. Slow-growing rodent ulcers, lip cancers, stone cancers, and the "locally malignant" ring cancers of the rectum, which occur in old age, are slow and less malignant, because they approach the normal tissue degeneration of old age.

Heredity occurs in some cases because some of the diseases in question must be regarded as merely pronounced variations of natural processes, and being major variations they are, as we have seen, prone to be transmitted. In popular parlance they are "freaks of nature," and are none the less so because they occur during post-natal instead of pre-natal life. Others are minor variations, and are, therefore, capable of being furthered or discouraged by all sorts of external influences.

Characters may be said to be transmitted in the order of their formation. They are deposited layer by layer, and that which was laid down last is most readily removed and is least likely to be passed on to the descendants.

All the diseases are *idiopathic* because the causes of development can only be conjectured. But though idiopathic in one sense, all of them must have their causes, and some of these, which have been termed "exciting" or "determining," are very obvious. These determining causes may all be grouped together into one class, for they are of such a nature as is calculated to produce depression of function and degradation of tissue. Alcohol, malaria, syphilis, lead, grief, shock, and over-fatigue all have a tendency to hasten senile changes, to bring about degeneration.

All are *progressive* in their course, because development itself is never stationary, and progression and retrogression are but phases of the same process. Life is not even, but is broken up into stages or periods. Hence the progress of all these degenerative diseases is subject to *interruption* or periodicity. They have but one termination, for they are *incurable*, and can no more be stopped in their progress than can the development upon which they are based. But just as the statement that they are without cause has to be

modified by the finding of indirect or exciting causes, so also may the statement that they are always lethal be similarly qualified. Various hygienic influences may be set to work to mitigate their consequences, or even to prevent their continuance, and possibly even to restore the affected organ to its natural condition. These influences are, all of them, such as are calculated to stimulate normal growth and development, and consist in such measures as change of air, sunshine, dry, bracing climates—in short, the exact opposite of those depressing influences which help to bring about or reveal the diseases. Among drugs, if we leave on one side remedies like iron and tonics, almost the only substance which has any influence in the direction of cure is *arsenic*. Instances of carcinoma, sarcoma, primary Bright's disease, pernicious anæmia, leukæmia, and many others of the group could be quoted in favour of its good effects.

Structural.—One important consequence of the reduction of cells to an inferior state, such as is implied in degeneration, is the rousing of the latent resisting or defensive forces of the body. By assuming a primitive form the degenerated cells are no longer in keeping with their surroundings. They are to all intents foreign elements, and inimical to the welfare of the body. Consequently the endothelial cells and connective-tissue cells already on the spot resume their primitive shape, multiply, and join with phagocytes from the blood and lymph to cope with the rebellion. They attack and clear away the decayed periphery of each cell, but cannot hurt the more vigorous cytoplasm which clings about the nucleus until that also has undergone molecular disintegration. They are also ineffective when cells have assumed an embryonic form without molecular deterioration, as is the case with cancer-cells, and, indeed, with many of the phagocytes themselves. But though unable to wear down the degenerated cells they can passively resist their encroachment. At any rate, this is the effect of their action in the case of cancers, for the fibroblasts, having done all they can, return to their normal resting state, and by so doing create an abundance of fibrous tissue which tends to contract and shut off the included cancer-cells, hindering their multiplication, and even in some cases compassing their destruction. But this same process carried out when the cells of an *organ* are degenerating is perhaps not quite so beneficent, for it is not possible to enclose a mass of cells in fibrous tissue so as effectually to isolate them without at the same time shutting off their function, and perhaps bringing about their strangulation. Hence the same process which is so salutary in the single cell degeneration of

cancer apparently adds to the damage which is produced by the similar deterioration of organs.

When we trace the disorders of growth and development back to their beginnings, we find that they are produced by two sets of circumstances: the one contemporary and consisting of such agents as the depressing emotions and toxins; the other historic or reversionary, that is, consisting in the reproduction of bygone impressions. These latter are termed *variations*, and are either progressive or regressive according as the circumstances from which they arose were calculated to facilitate or to impede development.

Variations may also be divided into two kinds according to their intensity. The more emphatic are termed discontinuous variations or mutations. Disorders of this stamp are not only of pronounced degree but are spontaneous, and sometimes hereditary. The less marked variations are termed continuous variations, or fluctuations. They are largely influenced by contemporary causes and are not hereditary.

If the views held here be correct, there is, as de Vries holds, a fundamental distinction between minor and major variations, for whereas the major variation is an indication that some higher stages of development have been dropped out (regressive) or exaggerated (progressive), in the minor variation a similar result is brought about in a totally different manner. In this variation the surrounding conditions reproduce in a concentrated degree the environment normal at a less advanced (regressive) or still more advanced (progressive) stage of evolution. At all events the conditions are calculated to act as an outside correlation either of a debasing and therefore retrogressive character, or of an elevating and therefore progressive character. In the one case the minor variation is of the nature of a reversion, and in the other it is like a hot-house plant stimulated and forced into a stage of development in advance of its fellows. In the one the variation (minor) appears in response to a congenial environment; in the other the variation (major) appears independently, without reference to environment. The environment suitable for the production of a minor variation of the kind now under discussion is of a depressant or irritant nature, and may act either from the outside or circulate in the fluids of the body or operate through the mind. Excessive toil, too long exposure to heat or cold, grief, physical, mental or moral shock are examples of so-called

external environment. Their effect upon the body is equivalent to that of the toxins. Examples of the environment which acts within the body evoking suitable minor variations of disease are furnished by alcohol, lead, and the poisons of syphilis, tubercle, enteric and scarlet fevers.

PART II

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF CELLS

I

INTRODUCTION

The distinguishing characters of a developmental or growth disease.—The object, hitherto mainly constructive, is now chiefly analytical. *Growth* disorders are affections of quantity; those of *development* are qualitative. They may be divided into groups, according to the tissue or organ concerned. The characters distinctive of infantilism and senilism are given, as well as their biological status as variations.

THE object of the first part of this book has been to subject disease in general to a rough examination, separating off those characters which correspond with the distinctive characters of normal growth and normal development, in order to use them as elements in building up the great class of the diseases of post-natal growth and development. Our aim has therefore been, in the main, one of construction. But in the course of this construction certain generalisations have appeared, which may be utilised for the purposes of analysis. By a process of reversion they become tests, and may be used for eliciting the nature of selected instances of disease. Or, like a sum in arithmetic, the truth of the answer is “proved” by reversing the method of working. So far our object has been chiefly synthetical; now it is mainly analytical.

Let us suppose that a certain disease is subjected to analysis. Our first task is to find out whether it is solely due to the action of some agent external to the organism, or whether it is, to a large extent, the result of internal causes. If the latter prove to be the case we are in the advantageous position of having put on one side a very large number of diseases to which the body is subject. We resemble the analyst, who, once having determined that he has to do with an inorganic salt, no longer has need to consider the larger group of organic compounds.

Our next step is to differentiate between (1) those diseases which affect individual cells, and (2) those which involve entire organs, or (3) have an effect which is not local, but is distributed over the whole individual. Having determined to which of these great subdivisions

our disease belongs, we then have to settle whether the condition we are considering is one of mere growth, which is mainly a quantitative change, or of development, which is mainly qualitative.

Let us, for the sake of argument, assume that the disease with which we are dealing is apparently spontaneous in its appearance; that it starts in single cells, and is a degeneration. We have now so narrowed the object of our analysis as to be able definitely to say that it is a cancer. But we have already learned that cancers are again divided into groups according to the tissue from which they arise. A cancer may spring from (1) epithelial cells and be a carcinoma; from (2) cells of connective-tissue origin and be a sarcoma; or (3) it may arise in endothelial cells, and as an endothelioma partake more or less of the characters of each of these groups; or, lastly, it may have its origin (4) in structures derived from the contained embryo or their analogues, and be a chorion-epithelioma. We find, by way of example, that the disease in question belongs to the epithelial group and is a carcinoma. But our knowledge of the construction of cancers tells us that carcinomata differ according to the particular kind of epithelium from which they spring. If from surface epithelium it is an epithelioma, a melanoma, or a rodent ulcer; if from the mucous membrane of the large intestine, a cylindroma and so on.

Now let us suppose that our developmental disease, instead of being one which affects cells, involves an entire organ. Then, just as we divided degenerations of cells into four main group, according to the tissue affected, so also may we divide the degenerations of organs into groups, according to the nature of the organs affected.

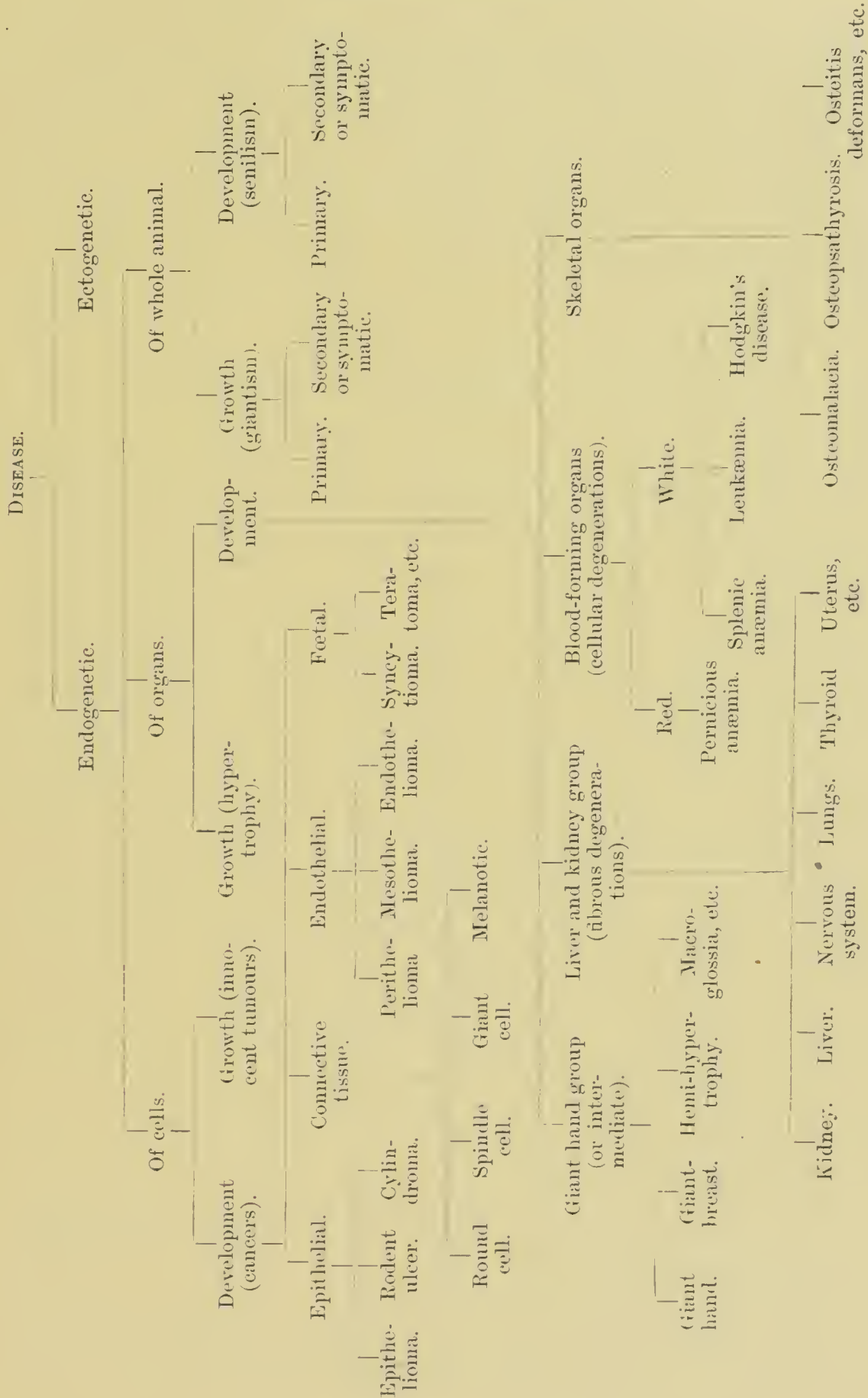
(1) We have first an early or intermediate group, consisting of certain diseases which lie on the borderland between the pre-natal and post-natal divisions, and between growths and degenerations, of which the giant hand is a good example.

(2) Then comes a fibrous or prosenchymatous group, which is distinguished by the formation of a great excess of fibrous tissue, as in fibrosis of the liver, kidneys, lungs.

(3) Next is a cellular or parenchymatous group, of which pernicious anæmia and leukæmia are examples.

(4) The fourth is the skeletal group, comprising degenerations of the bone and bone-marrow, of cartilage and of joints.

As in the case of the malignant degenerations of cells, the main divisions or genera of these organ degenerations are again divided into species, according to the organ at fault. Thus, if the disease we have in view be of the prosenchymatous group, it may be



a fibrosis of the liver or kidneys, or lungs, or brain, or spinal cord, or thyroid, and so forth. Lastly, each of these species embraces a number of varieties, of which the different kinds of liver fibrosis—intra-cellular, unilobular, multilobular, gummatous—are examples.

Instead of going to the facts of analytical chemistry for a simile we may draw up a plan of the divisions of the development diseases in the form of a genealogical tree, as on the previous page. But this, it must be understood, is for analytical purposes only, and is very incomplete.

How a Disease of Development is to be Recognised: The Tests.

We have yet to make a *resumé* of those characters which serve to distinguish the diseases of development as a class. These must necessarily vary according to whether the disease is a defect of development—infantilism—or is due to premature old age—senilism.

Infantilism.—The characters of infantilism are partly quantitative, partly qualitative. Organs so affected correspond in size and appearance with organs at some stage prior to the attainment of full growth. At the same time nutrition is depressed, so that such an organ is more vulnerable to the attacks of invading micro-organisms. Moreover, infantilism often results in premature degeneration, either of an entire organ or of individual cells (cancer), and is frequently associated with infantilism of other parts.

Senilism.—One of the most noticeable features of senilism is its infinite *variety*, for the disease may, like normal old age, begin in any constituent part of an organ. The difference which separates some of these varieties is so wide that the varieties are often mistaken for species. But all sorts of *intermediate forms* are met with, and it can always be shown that the differences between the different kinds are not specific.

Other characters of senilism are either functional (symptomatic) or structural.

Symptomatic features are in all cases of two kinds, to wit (*a*) generic, or those which are common to the group, and (*b*) specific, or those which are due to derangement of the function of the particular organ affected.

Generic or group symptoms are the only symptoms which need engage our attention at present. They have their basis on the physiological grounds of situation, age, sex, and the course and

termination of normal development. For reasons which have already been given, acceleration of development or senilism will be of gradual onset, sometimes hereditary, sporadic, and occasionally endemic, or with a tendency to become so. It will *vary in rate*, so that one form may be termed acute, and another chronic, and will favour one period of life in preference to another. Further, it will have *no adequate cause*, though at the same time certain toxins, especially lead, alcohol, and syphilis, and certain influences of inhibitory or depressing nature, such as grief, worry, and shock, may act as determining causes. It will be *progressive* in its course, though this progress will often be interrupted by periods of arrest or of temporary improvement. It will be *pernicious* in its effect upon the organ attacked, and will be *incurable* by drugs, though it may be improved by certain influences which are known to have an elevating, tonic, or stimulating effect on normal development. In addition it will not be contagious, though possibly the tissues which it affects may be implanted and grown in the tissue of an animal of the same species. Finally, it will be *present in the lower animal* as well as in man.

It will also be prone to come under the sway of certain physiological events, which, in the course of normal development, produce fluctuation of nutrition of growth and of development. These physiological events are more particularly those of the various *changes or climacterics* which separate from one another the periods of babyhood, childhood, youth, manhood, middle and old age. Women, in addition, will be influenced by the special changes of *menstruation*, *pregnancy*, and the *puerperal state*, and by that climacteric (menopause) which precedes the degenerative periods of middle and old age.

Lastly, as normal old age is a time of defective nutrition and of degeneration, so an organ affected with senilism is *more vulnerable* to the attacks of micro-organisms, such as those of tubercle and common inflammation; and it is also a *breeding ground for overgrowths and degenerations of single cells or cell groups*, such as adenomata among the former and carcinomata and sarcomata among the latter.

Structurally senilism is essentially a reversal of progressive development. It is a retrogression which has gone to a morbid excess and has assumed an aggressive character. The size, shape and other appearances which have been acquired by cells, in the course of their rise to some special position in an organ, tend to become altered, so that in senilism they become larger or smaller, or

misshapen. Their cytoplasm becomes more or less granular, or undergoes other molecular changes, causing it to react differently to colouring agents; their nuclei are also affected in regard to size, appearance and staining properties. Further, cells which are not special to the organ, but make up its framework, or cells which are not even attached, but have wandered into its interstices by means of the lymph- or blood-channels, are also implicated.

To put this into one sentence, it may be said that senilism consists in a reversion of cells on the one hand, and in an invasion of new cells of lymphoid order on the other hand.

From the *biological* point of view both infantilism and senilism are *variations* of a regressive character. Hence we shall find that all maladies which are true disorders of development occur in one of two forms. In one form the tendency to retrogression is less pronounced, while the influence of environment is of great importance. These correspond with the *continuous* or minor variations of the biologist. In the other form the tendency to retrogression is paramount, so that the disease reveals itself apparently without the help of any environment whatever, and may be hereditary. Disorders of this kind correspond with the *discontinuous* or major variations of the biologist, and are often hereditary. Variations of either kind, moreover, are prone to *associate* together, the frequency of such association bearing some relation to the normal *correlation* of the parts affected. In the case of major variations such association or correlation may be manifested in more than one generation (*familial association*). Among the organs most liable to undergo associated disorder or incapacity are the sex organs, so that all growth and developmental disorders of a major kind, though hereditary, are prone to terminate in *sterility*.

The foregoing constitute the tests by means of which we are able to say whether a particular disease is a disease of development or is not. Let us now apply them to the sarcomata, carcinomata, and other malignant tumours or ulcers: and further on to the giant hand, to fibrosis of the liver and other organs, to pernicious anæmia, leukæmia, and their allies, and to osteomalacia and osteitis deformans. If these and other diseases answer the tests, then they are diseases of development; if they do not, they belong to some other order of malady.

II

THE DISORDERS OF POST-NATAL GROWTH OF CELLS; INNOCENT TUMOURS.

Undergrowth.—This is of academic interest only.

Overgrowth: Innocent tumours.—Commonly termed *growths*. May be divided into two sorts, namely, those which appear during progressive, and those during regressive development. The former are probably progressive variations, the latter regressive. Growths are usually spontaneous in origin, but may be started by irritation. The spontaneous are discontinuous, the other are continuous variations. Their course is progressive, but interrupted, and terminable. Their structure is identical with that of the tissue from which they spring, modified by a mild degree of consecutive degeneration.

Undergrowth of Cells.

This is an affection of no importance, and is only of academic interest, for it cannot be distinguished from under-development of cells.

Overgrowth of Cells: Innocent Tumours.

When cells in their capacity as individuals undergo numerical increase beyond their normal limit, the result is a swelling, or tumour, or *growth*.

These growths or overgrowths may crop up in any part of the body. No tissues are exempt, though some are more liable than others. They also appear at all times of life, but if we regard them in a general aspect it is obvious that they are in reality greatly influenced by age. They tend to group themselves round the more pronounced phases of development, some favouring the progressive stages and others the retrogressive. Hence we may divide the overgrowths into two groups, according as they arise in progressive or retrogressive life.

1. Cell Overgrowths Originating during the Progressive Stages of Development.

Perhaps the best example is that of the chondromata which crop up around the epiphysal cartilages of the long bones during the

years of greatest cartilaginous activity. Similar outgrowths of bone also occur from osseous tissue under similar circumstances, and in both cases growth, as a rule, ceases so soon as the normal activity of their basic tissue comes to an end. Angeiomata are also peculiarly liable to appear during progressive development, and the same may be said of some papillomata, both naevi and warts being so closely associated with this time of life that we are too apt to regard them as almost exclusively children's ailments.

Of the angeiomata perhaps the most interesting are the multiple hereditary telangiectases. Professor Osler,* who has gathered together what information there is on the subject, says that "while the telangiectases may occur early in life, as a rule they are not noticed until later." They are of three sorts, the pin point, the spider form, and the nodular, and are to be found on the face, lips, tongue, palate, and sometimes on the limbs or trunk. But what is of most importance, giving the disease its chief character, is the fact that the dilated vessels are also met with in the interior of the nose, and that the bleeding to which they sometimes give rise may occur from the slightest possible injury, as in blowing the nose, or apparently from no cause whatever. Though this hæmorrhage seldom does more than produce anæmia, it may be so copious as to destroy life. The naevi may occur in the nose alone and account for some cases of epistaxis.

In one case the disease was found in the stomach, though it had never given rise to hæmatemesis.

We have ourselves seen one case, with Dr. Basil Martin, in a girl of twenty-five in which only two spider-like telangiectases were present—the one on the side of the nose externally and the other on the nasal septum. Both had bled, the latter pretty severely, and on three occasions. We cauterised them both with the actual cautery, with excellent results, for they were apparently destroyed, and the bleeding has never returned.

The disease has been mistaken for hæmophilia, and this is the more likely seeing that it is strongly hereditary. At the same time the heredity seems to affect both males and females impartially, and is not only familial, but can be traced from parent to offspring. Professor Osler advises treatment by plugging. A patient of his "had the ingenious device of a finger of a very thin rubber glove, which he inserted into the nostril, and by means of a small bit of rubber tubing he blew out the finger, turned a tap, and in this way successfully plugged the nostril."

* 'Quart. Journ. Med.,' vol. i, 1907, p. 53.

Another kind of innocent growths which appears during the progressive periods is the adenoma, such as that which constitutes the rectal polypus of young children.

In all these cases we associate the overgrowth with the activity of the tissue from which it springs, and regard it as evidence that such activity has exceeded its bounds. In other words overgrowths of this stamp are in all probability progressive variations. They are, as a rule, variations of such pronounced kind and are so abnormal that they are evidently major or discontinuous. Moreover, to settle any doubt as to their nature, no cause can be found for their occurrence, and they are often transmitted from parent to offspring, or occur among brothers and sisters.*

2. Cell Overgrowths Originating during the Retrogressive Stages of Development.

Among tissue overgrowth which break out during declining development are all those which have just been mentioned. After the middle periods of life have passed by, untroubled with such excesses, the onset of old age is characterised by the reappearance of cartilaginous, naevoid, and adenomatous outgrowths. The tumours of bone and cartilage no longer spring from the epiphyseal cartilages or from the shafts of the bone respectively, because these parts are now so inactive as to be little more than a mechanical framework. But at the joint ends of the bones, where differentiation exists, and use is still making its constant demands, any extraordinary activity of declining development is prone to be followed by tumour formation. This is especially noticeable when degeneration sets in prematurely, as in the disease arthritis deformans. Outgrowths of cartilage or bone may then be so numerous as to constitute the most striking feature of the malady.

Just as the outgrowths met with during progressive stages are expressions of the over-activity of advancing development, so these cell redundancies of retrogressive life are evidently an expression of that renewed activity which characterises the onset of old age. The one marks the period of childhood or youth; the other that of second youth or second childhood. In other words, the latter are the result of degeneration, and the same may be said of the angiomas, papillomata, and adenomata of old age.

These degenerative hyperplasias of tissue are equally, or even

* "Drs. Gossage and Carling have shown that the hereditary transmission conforms fairly closely with Mendel's law," 'Proc. Roy. Soc. Med.,' vol. ii, 1910, Med. Sec., p. 1.

more, pronounced than the hyperplasias which occur during progressive development, and are evidently, like them, as a rule, major variations. But whereas the progressive kinds mark a leap forward beyond the bounds of physiological restraint, the degenerations are due to too great a recession, and are therefore regressive variations. Though apparently to all intents and purposes of exactly the same nature, there is fundamentally as much difference between them as between the first childhood and the second childhood.

There is reason to believe that many other growths may be classified in the same way. Thus, the myomata of the uterus, though they occur, it is true, at all stages of uterine development, may be divided into those which appear when development is advancing, and those which first show themselves when development is on the wane. Similarly, it is possible that there are two kinds of lipomata, progressive and regressive, just as there is an obesity of childhood, and an obesity of the menopause.

But as a rule overgrowth is a product of degeneration. This is certainly true of most adenomata, such as those of the prostate, of the liver, and of the thyroid and pituitary bodies, and also of mollusca fibrosa and the fibromata.

Characters.

Ætiology.—A cause can rarely be traced for the presence of innocent growths, but occasionally they are undoubtedly the result of *irritation*. Perhaps the best example of this is the condylomata which form in parts bathed by irritating discharges, especially syphilitic discharges. Adenomata of the breast and myomata of the uterus are, less clearly, due to the irritation to which these parts are subjected in the course of their functional vicissitudes. Telangiectases may also be the result of friction, of cold, or of alcohol, as in “acne rosacea.”

Course.—This, as a rule, is progressive, but variable, so that it is rarely possible to estimate the size that any particular growth will attain in a given number of years. Growth may cease altogether for a time, only to start afresh after an interval. This feature is particularly noticeable in the myomata of the uterus, in the adenomata of the breast, in the lipomata and angiomas.

Event.—The prospects in all cases of redundant cell-growths are good. Though now and again a myoma, or a retroperitoneal fibroma, or lipoma, or a growth within the cranium, may endanger life by pressure on important organs, this is of rare occurrence. Enlarge-

ment usually ceases long before it has reached these dangerous proportions.

Treatment.—Beyond the removal of irritation no treatment is of any avail except the removal of the prominence. Growths occasionally disappear spontaneously, especially papillomata, uterine myomata, and angeiomata.

Structure.—The structure of a growth is in all important respects identical with that of the tissue from which it springs. At the same time the cells are arranged with less regularity, and are perhaps a little bigger or smaller than the cells normal to the part. If the growth be of gland-cells the deterioration of function which is implied in these differences is shown by the failure or partial failure of the adenoma to secrete.

Growths do not always consist of definite rounded accumulations of piled-up cells. In different cases all stages can be traced between them and overgrowths of entire organs. This is especially true of fatty collections, so that instances occur in which we cannot say whether the patient is affected with diffuse lipomata or with obesity. There are also all degrees of gradation between molluscum fibrosum and pachydermatosis, and between that and generalised dermatolysis.

Biological considerations.—Though overgrowths of cells must as a rule be regarded as discontinuous (major) variations, some are probably variations of the continuous kind. This is the case when they are not of pronounced character, and are the result of definite causes. Thus common warts are seemingly minor variations, and so are syphilitic condylomata.

But wherever heredity occurs there can be no doubt that we have to do with a variation of major degree. Hence, many adenomata and angeiomata, and probably myomata, are of this nature.

III

THE DISORDERS OF POST-NATAL DEVELOPMENT OF CELLS

DEFECTIVE DEVELOPMENT OR INFANTILISM OF CELLS

Defective development or infantilism of cells.—This is only of consequence as a precursor of degeneration (cancer formation).

DEFECTIVE development of individual cells, or of cell groups, is an academic disease of no particular importance, except in its bearing on cell degeneration or malignancy. We have already seen that there is good reason to believe that a cell or an organ, which has been stopped in the course of its progress towards maturity, is in a more unstable condition than is the normally developed organ or cell. Such a cell, or such an organ, is, in fact, far more likely to take on the changes of degeneration. It misses out certain stages of its life-history, and jumps from an embryonic or infantile stage to a senile. The only examples of defectively developed cells with which we are acquainted are those which are known as "rests." These rests are islands of cells, which, in the course of the development of an organ, have been separated from their mainland, and have become isolated among the uncongenial cell elements of a neighbouring organ. But as the significance of these cells lies almost solely in their liability to undergo degeneration it will be best to leave their consideration until the next chapter.

IV

PREMATURE DEGENERATION, OR SENILISM OF CELLS— CANCERS.*

Distinction between excesses of growth and premature degeneration of cells.

—Innocent tumours are *growths*, malignant tumours *degenerations*. The degeneration of innocent tumours is secondary to the overgrowth, as the growth of cancers is secondary to the degeneration. Growths are quantitative accumulations of cells, degenerations are qualitative. Growths begin with the rise, and end with the decline of the normal growth of their basic tissues; degenerations occur solely during declining development, and are interminable. Cancers are more vulnerable than overgrowths to the attacks of microphytes. Cancers are as various as the normal tissues from which they spring; though, in reality, all cancers consist of tissue reduced to its elemental simplicity. Transitional forms occur, and one kind is sometimes replaced by, or possibly transmuted into, another.

Distinction between Excessive Growth and Premature Degeneration of Cells.

WE have seen that the cells of the innocent tumour behave like the cells or tissues from which they originate, though to an exaggerated degree. But they cannot go to such extremes without undergoing some loss in the process. No abnormal excess of growth, whether of cells, or of the whole body, is possible without entailing some loss in those properties which make for evolution or development. Hence the tissue of every innocent tumour has undergone some impairment of quality.

When we turn to the cancer we see this great and striking difference, that whereas the innocent tumour is in the first place a failure in the restraints of growth, the cancer is primarily a failure in the process of development. There is in every cancer a retrogression of cells to a primitive condition. The presence of an embryonic type of cells is essential to malignancy, and the phenomenon of growth is merely one of its manifestations.

* The word "cancer" is used here and elsewhere as synonymous with "malignant disease."

The expansion of growth is indeed just as inevitable in receding development as expansion is inevitable when any liquid undergoes transformation into a gas.

Hence, to put it shortly, we may say that the only essential difference between an innocent tumour and a cancer is that in the former normal cells have undergone a change in quantity, whereas in cancer the change is qualitative.

The origin and course of a growth excess are largely determined by the normal growth of the part from which it springs. When the excess originates during the general impetus of advancing development it ceases so soon as its basic tissue has reached its normal equilibrium in adult life. When the excess originates during the renewed activity of developmental decline it stops so soon as the wave of degeneration, which gave rise to it, has passed over. Hence overgrowths are not only composed of the tissue upon which they grow, but share in its physiological changes. Cancers, on the other hand, arise only as the outcome of declining development, diverge widely from their parent tissue, and continue to live and proliferate independently.

Another, though secondary, difference between innocent growths and cancers consists in the fact that whereas innocent tumours maintain their vitality almost unimpaired, and form rounded masses of tissue without break of surface, the cancers are often less tumours than ulcers, for their cells are not only choked to death by overcrowding, but readily succumb to the attacks of micro-organisms. This vulnerability is a senile feature, for the phenomena of old age point to the conclusion that any organism which recedes to an embryonic condition is necessarily more assailable by its enemies, big or little.

The Varieties of Cell Senilism and their Essential Unity.

The different sorts of cancer form one class, or group. In this group the *carcinomata* and *sarcomata* stand out most conspicuously. They were, not long ago, regarded as invariably and fundamentally distinct diseases, but the tendency of recent research is to throw doubt upon the reality of this dissonance. Thus pigmented neoplasms originating in the epiblastic skin and choroid, and usually regarded as sarcomata, are now believed by some observers to be carcinomata. Dr. Woods Hutchinson shows that the gliomata, which spring from neuroglia, and are therefore ectodermal in origin, must be classed with the carcinomata, though they resemble sarco-

mata in appearance and have hitherto been so regarded. And, lastly, other forms of cancers have been brought into view, and the study of some of these has furnished connecting links. This is more especially the case with the *endotheliomata*, concerning which some authorities hold that they are closely related to the carcinomata, while others would classify them with the sarcomata, though it is, we believe, usually held that they show points of resemblance to both of these degenerations, for while their alveolar cell groups partake of the nature of epitheliomata, the connective tissue between the groups is sarcomatous in appearance.* Their relation to the sarcomata is dwelt upon by Dr. Woolley,† who has been able to show, by means of the improved method of staining introduced by Dr. Mallory, that the beginnings of fine fibrils can be detected between the endothelial cells. Dr. E. J. Wood‡ has given details of a case in which a growth of one testicle was found on microscopical examination to be a large round-celled sarcoma, whereas growths of the kidney, liver, and lungs, apparently secondary to it, proved to be endotheliomata. No less than five years elapsed between the first appearance of the cancer and the death of the patient. A case will presently be referred to in which the primary growth was carcinomatous and the secondary growths were sarcomatous.

The transitional nature of the endotheliomata is still further emphasised by Drs. H. D. Rolleston and Grünbaum's case of perithelioma of the colon, of which the "striking features were the transitions from cells of a sarcomatous type to cells exactly resembling columnar epithelium."§

In an exhaustive paper brought before the association of American physicians in 1902, Professor Adami and Dr. Woolley,|| dealt with an intermediate form of cancer furnished by tumours which spring from that part of the mesoblast which eventually lines the body cavities and forms the ovaries, testes, kidneys, suprarenals. The tumours in question are by them termed "mesotheliomata," and they describe such a tumour occurring in the adrenals and refer to twenty other instances which have been placed on record. The tumours are carcinomas in regard to their histology. Yet secondary masses found in the lymph-glands, lungs, and brain, showed all the

* See Max Borst, 'Die Lehre von den Geschwülsten,' Bd. ii, S. 295.

† 'Johns Hopkins Hosp. Bulletin,' January, 1903.

‡ 'Amer. Journ. Med. Sci.,' vol. cxxx, 1905, p. 643.

§ 'Trans. Path. Soc.,' vol. liv, p. 353; also vol. xlviii, 1896, p. 259.

|| 'Trans. Assoc. Amer. Physicians,' vol. xvii, 1902, p. 621, "A Primary Carcinomatoid Tumour (Mesothelioma) of the Adrenals with Sarcomatous Metastases."

characters of round or spindle-celled sarcomata. The authors conclude that "tumours of mesothelial origin may vary in type in their primary growths and in their metastases, and these variations are evidences, in reverse, of the various stages in the genesis of the tissue in which the tumours originate."

The **chorion-epitheliomata** or syncytiomata are, as their name implies, of foetal origin, and usually have their beginnings in the degeneration of chorionic villi. They are peculiarly liable to appear after the formation of hydatidiform moles. Examined under the microscope these tumours are found to consist, in the main, of large decidual cells, chorionic villi, and multiplicates of the cells of Langhans' layer and the syncytium. They occur not only in the parous uterus, but have also been found in the virgin uterus, lungs, heart, testes, ovaries, and the mediastinum.* Under these latter circumstances it is pretty certain that they have arisen from cells of teratomatous origin, and it is the opinion of some observers that a few uterine cancers are also due to this cause, particularly those which are found in the uterus of young girls.

Dr. Victor Bonney,† who describes a case of pre-natal origin, shows that the constitution of chorion-epitheliomata varies according to the character of the cells from which the particular growth happens to be derived. Hence he divides them into the Langhanseomata, consisting chiefly of small hyaline cells derived from Langhans' layer; the malignant syncytiomata, made up of masses derived from the syncytium; and choriomata, arising by proliferation from the foetal ectoderm, and containing villi in a state of vesicular degeneration.

Those that do not have their origin in chorionic tissue are thought invariably to arise from teratomata, and Dr. Bonney gives reasons for his opinion that in this latter event the teratomata contain elements of the trophic ectoderm, which corresponds with the trophoblast of chorionic villi.

Malignant granulomata.—There is another instance in which tissue not commonly present in the body is prone to undergo malignant changes. This is granulation-tissue. Granulation-tissue is, like chorionic tissue, a temporary structure, and consists of cells which recapitulate, after a rough and imperfect manner, the phases of development which have been passed through by the particular organ in which the repair is in progress. But, for the time being, such tissue is obviously just as much alien to its surroundings as is the decidual tissue. Hence, it may become excessive and be heaped

* Dr. Ritchie's well-known case, 'Lancet,' 1903, vol. ii, p. 1743.

† 'Trans. Path. Soc.,' 1907, vol. lviii, p. 9.

up into tumours. These tumours are innocent as a rule and do not return after they have been taken away, but some of them do so return, and will presently be referred to as on the debatable ground between innocence and malignance. Occasionally one of these neoplasms will pass over the borderland and prove itself to be definitely cancerous.

Mixtures of sarcoma and carcinomata.—Sometimes carcinoma and sarcoma exist side by side in the same organ. At others they are mixed together, so that in the same tumour one finds sarcoma in one part and carcinoma in another, or the two are intermingled. Dr. Spencer* agrees with Gusserow and Opitz that a careful examination of all sarcomata would prove that the association of these two forms of malignancy is less rare than is thought.

As yet there does not seem to be sufficient evidence to prove that sarcomata and carcinomata may be transmuted one into the other. Though Leopold† says that on one occasion he transplanted some cancer-cells from a carcinoma of the ovary into the tissues of a rat, and that an adeno-sarcoma formed at the point of inoculation, yet this experiment stands alone, and has apparently never been confirmed.

Dr. Bushnell‡ asserts that, in a cystic sarcoma of the breast, or “adeno-cysto-sarcoma” of Ericson, he has traced the columnar cells of many intra-cystic growths by continuous and gradual transitions into large sarcomatous elements. Also in commenting upon a huge diffuse melanotic sarcoma of the liver, secondary to a pigmented mole, he says that he “regarded the cells in the liver as showing transitions from small endothelial to large sarcomatous elements.”

The difference between the various forms of cancer seems to be one of site. In other words, they all have the same pathology, but vary according to the locality in which they are found, and the greater the distinction between the forms of tissue in which they originate, the wider the difference between them. This is well exemplified in the carcinomata, which owe their special characters to the fact that they spring from a class of tissue which has a pronounced individuality. But all epithelium is not alike. There are marked differences between the character of the normal epithelium of different parts, and so also we find differences between the cancers which spring from them. The cylindroma of the intestine is easily to be distinguished from epithelioma of the lip, and the scirrhus

* ‘Trans. Obstet. Soc. London,’ 1905, vol. xlvii, p. 338.

† ‘Proceedings of the International Congress, Paris,’ “Etiologie des Carcinoms,” vol. iii, 1900, p. 143.

‡ ‘Lancet,’ 1904, vol. i, p. 752.

cancer of the breast is a very different disease from the carcinoma peculiar to the thyroid gland. Hence, there is a great range of variability, for each of the constituent tissues of any part of the body may give its impress to the cancers which originate in it.

Thus, to mention one example, Darier,* in his work on skin diseases, divides the epitheliomata into seven forms, namely—(1) papillary; (2) horny; (3) cicatricial; (4) rodent; (5) adenoid (lobulated encapsuled tumours like a gland, generally derived from benign growths); (6) carcinomatous (of the alveolar type); (7) multiple senile or “*acné sébacei concrète vel kératome sénilis*.” This last arises in connection with sebaceous glands, or acne, or multiple senile warts.

So in like manner with the sarcomata, the endotheliomata, and the syncytiomata. Hence, a sarcoma which springs from a pigmented mole, if, indeed, it be a sarcoma at all, is markedly different from a sarcoma of one of the nasal fossae, and a sarcoma which grows beneath the periosteum (periosteal sarcoma) differs from that which grows upon it (parosteal sarcoma), and that, again, is very different from the sarcoma which starts in the marrow (endosteal sarcoma). It is therefore very evident that the degeneration of cells in cancer is never carried to its ultimate limits of complete independence, for the cells always show some vestige of restraint. It never consists in a mass of rampant cells which have entirely lost their identity and are without form or character, but always show marks of the organ from which it grows. Further, the secondary manifestations also tend to mimic the characters of the organ in which they originate. In no case do they seem capable of entirely divesting themselves of habits acquired by long successions of generations of order and restraint.

Distinction between the cancers of youth and the cancers of old age.—There is reason to believe that, from a pathological point of view, cancers which start in young life (say, during the stages of progressive development) should be distinguished from those which are grouped round the declining periods of life.

Those of the progressive period are as a rule due to the consecutive degeneration of cells in a state of infantilism.

They are distinguished not only by their early appearance, but by their greater malignancy and by their tendency to show hereditary influences.

All cancers which spring from cell rests and from vestigial structures are of this class, and so are the chorion-epitheliomata. An

* ‘*La Pratique Dermatologique*,’ vol. ii, p. 116.

excellent example of this class of cancer is furnished by retinal gliomata.

Mr. Bland-Sutton * says that " Mr. Treacher Collins has drawn attention to the great similarity which exists between the cells composing the retina of the fœtus at the third month, when its layers are undifferentiated, and the tissue of the retinal glioma."

This may of course mean either that the retinal cells have degenerated back to this fœtal condition, or that the cancer springs from cells of immature type. These gliomata occur exclusively in children, are often congenital, and many hereditary cases have been reported.

* 'Tumours, Innocent and Malignant,' p. 161.

V

CLINICAL CHARACTERS OF CANCERS

Cancers are sometimes started by irritation, mechanical, chemical or thermic, including that produced by syphilis, alcohol and arsenic. Though as a rule not capable of transmission, the *hereditary* element is sometimes present, the heredity being usually of the family type. Cancer, being a developmental condition, is largely influenced by the normal vicissitudes of declining development incidental to sex, and perhaps to those of geographical, social, racial and zoological origin. The *course* of cancer is progressive, but variable or interrupted. Intermittence is sometimes so extreme that the cancer disappears. The recovery may apparently be consequent upon incomplete removal. Nevertheless, the prospects of recovery are so slight that all cancers may be regarded as lethal, unless they are eradicated. Cancer-cells are more vulnerable than normal cells. Hence they may be destroyed by X rays and radium rays, or by means of certain toxins. Arsenic is also of some remedial value. Removal of the ovaries is probably of indirect value in breast cancers by increasing the senility of the whole breast.

Ætiology.

CANCER used to be regarded as one of the most *idiopathic* of all diseases, but increasing knowledge has tended to modify this view. It is now recognised that the abuse of the clay-pipe, *prolonged irritation* by arsenical soot and other irritants, such as X rays, lupus, retained secretions, may act as exciting causes. It is popularly supposed that cancer may be caused by *injuries*, though Cohnheim* denied that this ever happens. But Berger,† who has gone into the subject very carefully, concludes that there is some ground for the supposition. A form of injury believed to be especially prone to produce cancer is a succession of contusions, or repeated irritation acting upon tissues already in a condition of mild inflammation. A good instance of cancer being started by a blow is mentioned by Dr. Mason.‡ A man received a heavy stroke from a cudgel upon his right arm just below the shoulder, with the

* 'Vorlesungen über Allgemeine Pathologie.'

† 'Vierteljahrschrift f. gericht. med. u. öffentl. Sanitätswesen,' Bd. xiv.

‡ "Some Remarks upon an Analysis of 5000 Cases of Deaths from Malignant Disease," 'Brit. Med. Journ.,' 1901, vol. i, p. 1199.

result that a large hæmatoma formed. The swelling went down so gradually that after five weeks it was still as big as a hen's egg. It then began to swell again, and was eventually found to be sarcomatous. The limb was amputated at the shoulder-joint, but the cancer returned.

We once removed a cancer which arose from a similar cause in a similar place. The patient was a lady, aged 58 years, who was sent to us by Dr. Walter, of Wallingford. There had been a blow near the insertion of the right deltoid muscle, and the cancer appeared on the same site soon after the bruise had faded away. When we saw it with Dr. Walter there was a soft, boggy, pedunculated, rounded lump resembling a sponge both in shape and consistency. We cut it away with its surrounding tissues, and on examining it under the microscope found that it was an epithelioma. It recurred in the axillary glands and caused the death of the lady about eighteen months afterwards.

In another case a lady, aged 72 years, knocked her forehead against the corner of a mantel-piece as she was rising from a stooping position. We saw her shortly afterwards and found a bruised cut on the left temple. This did not properly heal, and in about three months became the seat of a cancer, which was removed. Other growths then sprang up almost simultaneously in different parts of the body. These were not ordinary epitheliomata, but resembled alveolar carcinomata (alveolar carcinomata of Darier). They showed little tendency to spread or to ulcerate widely, but manifested themselves mainly by bleeding. Some of them bled profusely. Dr. Marriott saw her with us on one occasion. The old lady gradually sank, apparently not so much from the effects of the cancer as from senility. After death an examination of the body failed to reveal any internal cancer.

Local irritation is now admitted by most authorities to be a very potent cause of cancer. Well known examples are the cancers which appear about the waists of Thibetans as the result of burns from the tinder boxes which they carry in their waist-bands; the cancers of the penis of Cingalese, due to the accumulation of dirt under their long foreskins, and the cancers of the mouth which are prevalent among both men and women addicted to betel chewing.

Syphilis.—Among the causes of cancer syphilis must be included. Sir Jonathan Hutchinson, writing on this subject, says*: "I am sure I have repeatedly seen the syphilitic ulceration of inflammatory hypertrophy glide into cancer so imperceptibly and gradually that

* 'Brit. Med. Journ.,' 1883, vol. i, p. 554.

I could not tell when the one ended and the other began ; but my impression is strong, as I have several times before publicly stated, that parts formerly affected by syphilitic inflammation possess a special degree of proneness to take on malignancy."

Alcohol.—There is no clear evidence that cancer in general is due to the drinking of alcoholic intoxicants.

Dr. Snow,* in common with many other observers, believes that alcohol has a conspicuous share in giving rise to cancer of the lips and tongue. It often acts in conjunction with mechanical irritants and syphilis.

Sir Victor Horsley, writing upon this subject, says : "There is a great excess of disease in persons employed in those occupations in which alcoholic indulgence is common. According to the Registrar-General's figures, the same number as would furnish 44 deaths from cancer among all occupied males, 35 among clergymen, and 43 among doctors, would furnish 63 deaths from cancer among commercial travellers, 70 among London innkeepers, and 70 among brewers. In an investigation which I made as to the persons insured in the United Kingdom Temperance and General Provident Institution, I found that the same number living at the same ages which gave 100 deaths from cancer among the non-abstainers only gave 71 deaths among the abstainers. This is not surprising when we remember that one of the factors producing cancer is the influence of chronic irritation, and alcohol causes irritation of the tissues with which it comes into contact.†

Arsenic.—Sir Jonathan Hutchinson believes that arsenic must be regarded as an influential cause of cancer, and that the scrotal cancer of the chimney-sweep is almost certainly due, not to the soot, but to the irritating particles of arsenic which is sublimed with it. He thinks cancer may also result from the internal use of arsenic, and mentions many cases of the appearance of cancer in the subjects of psoriasis and of other diseases for which arsenic has been taken for long periods continuously.

Age.—The origin of cancer is largely determined by age. Connective-tissue degenerations (sarcomata) tend to appear during all stages of development, while the carcinomata arise during the retrogressive periods.

There is reason to believe that cancer occurring in early life runs a quicker course than when it begins in old age. This is most

* 'Lancet,' 1904, vol. ii, p. 822.

† 'Alcohol and the Human Body,' by Sir Victor Horsley and Dr. Mary Sturge, p. 353.

evident when a young man or woman, the offspring of a parent with cancer, is affected with the same kind of disease. It is then obvious that the cancer is more virulent in the younger individual.

Heredity.—The occurrence of cancer in more than one member of the same family has, until recently, been attributed to the influence of heredity, and Sir Jonathan Hutchinson believes that, when so inherited, it tends to occur earlier in life; that is to say, that if a parent die from cancer and his son become cancerous, the disease shows itself at an earlier age in the son than in the father. A striking example of this characteristic is referred to by Dr. Woods-Hutchinson,* who has known a son die from carcinoma some five years before the appearance of the same form of cancer in the father.

But Professor Karl Pearson† has shown pretty conclusively that an analysis of statistics, if properly made, does not support the opinion that cancer is hereditary. He compared the histories of 3000 cancerous with the same number of non-cancerous patients, and found there was practically no difference between them in respect to the prevalence of the disease among their relatives.

Notwithstanding this expert opinion, there must still remain in the minds of most of us the impression that in rare instances cancer does occur in families as the result of heredity, though it is not easy to see how these hereditary cases escape through the meshes of the statistical net.

A good examples of apparent heredity has been recorded by Mr. Childe, of Portsmouth.‡ In this case, out of a family of four sisters and one brother, three sisters between the ages of thirty and thirty-five were suffering at the same time from carcinomata of the rectum. In two of them the carcinomata had supervened upon multiple polypoid adenomata; and there was reason to believe that the father had also died from rectal cancer, for it was ascertained that his death had resulted from some rectal disease associated with fistula. In view of the rarity of cancer of the rectum in women it seems, at first sight, that this conjunction could not possibly have been due to any influence but that of heredity. But the force of this argument is somewhat weakened by the researches of Mr. Childe, which show that the hereditary factor exists in the adenomata rather than in the malignancy, for the former disease often occurs in different members of the same family, is often directly inherited,

* 'Human and Comparative Pathology,' p. 206.

† 'Archives of the Middlesex Hospital,' vol. ii, p. 127.

‡ 'Brit. Med. Journ.,' 1905, vol. ii, p. 804.

and is very prone to undergo malignant degeneration. At the same time it is remarkable that four members of the same family should be afflicted with cancer, whether it proceeded from some prior tumour or did not. Sir Jonathan Hutchinson says that "an innocent tumour may, under the influence of heredity, become exaggerated and made to occur earlier in life or to be transmuted into one of undoubted malignancy.*

Broca,† writing in 1866, states that he can vouch for the occurrence of cancer beginning in a lady, destroying her four daughters and six out of seventeen of the third generation. This well-known example is quoted by Drs. Hillier and Fritsch.‡ The latter also refers to the statistics of Roger Williams,§ and his account of the Napoleon family. Napoleon, his father, his brother Lucien, and two sisters all died from cancer of the stomach. This is the more significant, inasmuch as the part selected by the disease was very unusual, at any rate in women. The only weak spot in the account is the age of the record, leaving room for question as to whether the disease was really cancer.||

There are other instances published of the occurrence of cancer in so many members of the same family that the possibility of attributing the association to chance or to any other circumstance than sheer heredity seems entirely out of the question. Gliomata of the retina are peculiarly prone to occur hereditarily. Dr. Newton¶ has published an instance of the occurrence of glioma in a child of two, the youngest of a family of sixteen. Of this family nine had suffered from glioma of the retina before the age of three, and all had died except one, who was operated upon for unilateral glioma, and died from its recurrence at the age of five. Three were unilateral and five bilateral. Five were in males and four in females.

An equally striking instance of the family occurrence of cancer of another part is recorded by Dr. Watkins, of Lincoln.** In this case the grandfather and grandmother had both died from senile

* 'Hutchinson's Archives,' 1896, vol. vii, p. 25.

† 'Traité de Tumeurs,' p. 151.

‡ "Heredity in Cancer," 'Second Report from the Cancer Research Laboratories of the Middlesex Hospital,' vol. ii, 1904, p. 104.

§ 'On the General Pathology of Cancer.'

|| In his 'Annual Report of the Museum of the Royal College of Surgeons of England for 1910' (p. 5), Professor Keith says that two specimens supposed to represent secondary growths of cancer in the bowel removed from the body of Napoleon I, and probably authentic, proved to be, not carcinomatous, but enlarged lymphatic follicles containing extravasated blood, most likely the result of senility.

¶ 'Australasian Medical Gazette,' May 2nd, 1902, p. 236.

** 'Brit. Med. Journ.,' 1904, vol. i, p. 190.

decay. They had four children, of whom one was a female, who died from stone cancer of the breast. Of the males there was presumptive evidence of cancer in all three, for the first died after an operation for obstruction of the bowels, and the second and third from disease of the rectum accompanied with piles. But in the third generation this evidence of cancer was no longer presumptive but was very explicit, for of the five children of the second son all but one died from cancer, and this one, a female, was at that time suffering from cancer of the rectum. One of her sisters died from cancer of the womb, one from cancer of the breast, and both brothers from cancer of the rectum.

It will be noticed that in the first of these two instances the inheritance was of the family type, and that in the second it was both familial and by direct descent. In both cases the number and proportion affected were so large, and there was such a strong tendency for the disease to affect the same parts (to wit, the retina in one case and the rectum and reproductive apparatus in the other), that no other explanation than that of heredity seems quite satisfactory.

Sex.—One important factor in the causation of cancer is *pregnancy*. This undoubtedly largely accounts for the preponderance of cancer among women. It is generally held that pregnancy is not only conducive to the after-appearance of cancer of the breast and uterus, but also exerts an unfavourable influence upon the course of existing malignant disease, when the part affected is one of the organs of reproduction. Thus in a case of hard cancer of the vagina in a pregnant woman, reported by Kaiser,* he was of the opinion that the pregnancy caused the cancer to take an acute course. But there is much difference of opinion on this subject, and Leopold, among others, believes that pregnancy has no such effect. The pregnancy seems to act partly as a local irritant and partly by setting up violent fluctuations in the growth and development of the uterus and so rendering its tissue unstable. Yet a third reason will be referred to presently.

According to Dr. Lazarus Barlow,† 80 per cent. of all cancers in males are of the alimentary tract, whereas in 80 per cent. of all females they affect the organs of generation and lactation. But in both sexes the generative system is usually attacked first and the cutaneous system comes next. Before the age of thirty-five cancer is more common in women than in men.

* 'Zeitschrift für Gynäkol.,' No. 27, 1904.

† 'Fourth Report from the Cancer Research Laboratories of the Middlesex Hospital,' vol. v, 1905, p. 46.

There is a common belief that cancer is associated with *overwork, poor food, poverty, and hardship* in general.* But much of this evidence is invertebrate, as it consists of impressions only, and is not supported by any column of statistics or other back-bone of ascertained facts. Nevertheless, it cannot be ignored, for it is very difficult to deal with such circumstances as these in a way that will satisfy the mathematician. Some well-known authorities have held the opinion that the above factors, as well as *prolonged anxiety, disappointment*, and other depressing conditions or emotions, conduce to the appearance of cancer.

Trousseau, who himself died from cancer of the stomach, attributed the disease in most cases to excessive fatigue of mind and body, as well as to irregularity and haste in meals,† and Sir James Paget, as well as many other careful observers, have expressed similar views. Of the same import also is the opinion held by some writers that good food, cheerful society, sunny climates, chalk downs, and the healthy open country in general, are inimical to the appearance of malignant disease.

Sir William Bennett has described two cases in which mental concentration directed to the breast seemed to have taken part in the causation of cancer of that organ.‡ But such causes as these are too indefinite to be capable of proof. One must be content with the bare statement of opinion, for there seems to be no convincing evidence either one way or the other.

Civilisation; race; zoological distribution.—It has long been observed that cancer is apparently much more common among the civilised than among the half-civilised or savage, but it is now doubted whether this observation is correct; or if correct, whether the diminished liability is due to civilisation or to race.

In an investigation made by the Colonial Office on the prevalence of cancer in the Colonies,§ it was reported by different medical officers that cancer is rare or unknown in a number of colonies where there is a large native or aboriginal population, such as British Central Africa, British East Africa, the Gold Coast, and Mauritius. In Ceylon cancer is a comparatively scarce disease, one death from this cause occurring in every 16,820 persons living in 1903 as compared with one to 1400 in this country.

Of course, in none of these cases is the opinion or statistical

* See Dr. Sinclair, 'Brit. Med. Journ.,' 1902, vol. ii, p. 321.

† 'Brit. Med. Journ.,' 1905, vol. i, p. 795.

‡ "Behaviour of Certain Malignant and Innocent Growths," 'Lancet,' 1899, vol. i, p. 491.

§ 'Lancet,' 1905, vol. i, p. 655.

evidence absolutely satisfactory, for there are other factors, such as the highly important one of age, to be taken into consideration; but, so far as they go, they are suggestive of race or civilisation having some influence on cancer prevalence.

One fact brought out in these reports is pretty conclusive as to the reality of the action of local causes in giving rise to local peculiarities. Sir Allan Perry, Principal Medical Officer of Ceylon, shows that in that country cancer is more prevalent among men than among women, that the most common site is the mouth (which accounts for no less than 55 per cent.), and that this preponderance is not confined to men, but is nearly as marked in women. The next most common situation is the penis, which is affected in 32 per cent. In all these ways cancer in Ceylon behaves very differently from cancer in Great Britain. This difference seems to be accounted for by the betel-chewing habits of the people on the one hand, and by the absence of the rite of circumcision, combined with dirtiness on the other.

That the scarcity of cancer among the uncivilised may be an affair of *race* and not of habits or civilisation is suggested by certain investigations among civilised blacks. Thus it has been shown by Dr. Billing, in his report on the tenth census of the United States,* that the death-rate from cancer among negroes is less than half that among whites. An objection may be made to this interpretation on the ground that the negroes live shorter lives, and the figures are therefore gathered from a younger population—a population which is on that account less liable to cancer.

Drs. Bashford and Murray,† in making an investigation in connection with the Cancer Research Fund, find that cancer occurs in many, if not all, kinds of vertebrate animals, but that, so far, no invertebrate has been known to be affected. Cancer can be successfully transplanted from one animal to another of the same species, but not to an animal of another species.

Course.

Cancer varies greatly in its rate of extension. It may be so rapid as to simulate inflammation. Indeed, quickly growing sarcomata accompanied by redness and pain have often been opened in mistake for abscesses.

On the other hand, cancers are sometimes so slow in their pro-

* Quoted by Dr. Woods Hutchinson, 'Human and Comparative Pathology,' p. 265.

† 'Lancet,' 1904, vol. i, p. 413.

gress that they make very little headway, even after they have been in existence for years, and are prone to be mistaken for fibromata.

Their rate of growth is largely influenced by the surroundings. If adjacent cells be also more or less on the verge of degeneration, as in old age, the progress is, as a rule, very slow. If, on the other hand, the neighbouring cells are engaged in the activity which we associated with progressive development, then the progress of the cancer is, as a rule, greatly accelerated. The difference seems to depend upon the suitability of the environment. When the surroundings are congenial the progress is slow; when they are uncongenial the progress is rapid. It is, perhaps, never more rapid than when the cancer attacks the lactating breast, and never slower than when it forms in the useless senile breast, as the "stone cancer" of old women.

All forms of cancer are more prone to appear in those organs which naturally undergo rapid changes, like the breast, and the glands in the cervix of the uterus, than in those which are comparatively stable in their development, like bone, cartilage, and muscle.

Cancers show at times the peculiar feature of being temporarily delayed or stopped in their progress, and these phases of arrest or of increase may alternate more than once before the disease finally puts an end to existence.

Such periods of remission account, to a very large extent, for the supposed efficacy of violet leaves, Matteism, and other so-called cancer cures. Despite these delays the course of malignant disease is *progressive*. Dr. Bashford has referred more than once to the evidence that cancer growth in an interrupted and not a continuous process,* and this point is also insisted upon by Dr. Max Borst.† Dr. Bashford,‡ again, has noticed that cancer transplanted from one animal to another still continues to show periodic fluctuations. These fluctuations affected the success of some of the transplantations, and coincided with changes in the histological character of the tumours. Just as the rate of growth of a cancer varies, so the tendency of the same individual to the formation of cancer also varies, and to a like degree. His tissues may be susceptible to this form of degeneration at one time and not at another, and these variations are not necessarily synchronous with those general variations which we term changes of life.

In some cancers the fluctuations are so pronounced as to constitute

* 'Trans. Med. Soc. Lond.,' 1905.

† 'Die Lehre von den Geschwülsten,' Bd. i, S. 49a.

‡ 'Report of the Imperial Cancer Research Fund,' No. 2, p. 2.

their chief characteristic. The sarcomata are especially prone to be of this kind. We have seen two well-marked examples.

We once saw with Dr. Johnstone, of Reading, a lady of between forty and fifty, of chlorotic appearance, and rather obese, in whom a large sarcoma of the nape of the neck seemed completely to disappear, but afterwards returned and destroyed life.

In another case seen with Dr. S. Gilford the growths were abdominal, and were collected in the lower abdomen round about the uterus. An abdominal section was carried out with the object of removing them, but they were so numerous and so matted together that the operation was not completed. Moreover, though some of them stood out as conspicuous rounded nodules, like small potatoes, they were in every case covered with what appeared to be the coats of the intestines stretched over them, so that we did not feel justified in cutting into them for purposes of microscopic examination and could not therefore confirm our diagnosis.

They were of uniformly firm consistency, did not appear to be tubercular, nor were they merely enlarged glands. The growths became worse after the operation, until they filled the lower part of the abdomen, and projected in visible lumps on the surface. The patient also became very thin and weak. A marvellous change for the better then took place, the growths rapidly subsided, she took her food well, became stronger and fatter, and actually resumed her work as a nurse. At the same time the growths never completely disappeared, and three weeks ago another wave of recurrence set in. This was apparently started by a week of hard work with very inadequate rest. She is now troubled with vomiting, pain, emaciation, constipation, and increasing fulness of the abdomen.

In some cases of cancer the spontaneous improvement may be so pronounced and so protracted as to throw doubt upon the truth of the diagnosis. But as a rule the disease soon sways back to its former position, or goes more or less beyond it. But this is not always the case. Many instances have now been recorded of the *spontaneous disappearance* of malignant tumours, such as those of Pearce Gould,* Osler,† Prickett,‡ and Waring.§

In some of these the cancer, which had been so diagnosed on the best of evidence, entirely disappeared without apparent cause; in others, after a simple exploratory operation; and in yet others after

* 'Clin. Soc. Trans.,' vol. xxx, p. 205.

† 'Canadian Practitioner,' 1900.

‡ 'Brit. Med. Journ.,' 1903, vol. i, p. 915.

§ 'Med. Soc. Trans.,' vol. xxviii, 1905, p. 210.

a small piece had been cut out for histological examination. It has chanced on not a few occasions that a diagnosis of cancer has been made and the patient forthwith sentenced to death; and yet, the cancer has shrunk away and never returned. It therefore behoves the surgeon never to pronounce a cancer hopeless unless the patient is actually moribund.

We have seen two such instances of recovery from inoperable cancer. One was of a patient of Dr. Murrell, of Reading. The cancer was a diffuse carcinoma of the gall-bladder. At the operation the gall-bladder was found to be uniformly thickened, and was so adherent to all the adjacent parts that it was hopeless to attempt its removal. Its walls were quite 3 cm. thick, and the internal surface was uneven, like the cobbles of a pavement. There was no biliary calculus inside. A piece was cut out and was found to be a spheroidal-celled carcinoma. Though we did the operation nearly five years ago, the patient is vastly better in health, and all signs of the tumour have disappeared.

Sir Wm. Bennett* has given an account of a similar case, not of carcinomata, it is true, but of mixed spindle- and round-celled sarcoma, growing in the same region of the abdomen. This also disappeared after exploration and removal of a piece for histological examination. It occurred in a woman, aged 36 years, but it could not apparently be ascertained whether it was or was not of the gall-bladder, though it occurred in that region. It also invaded the liver and omentum.

At other times the tumour removed, and found to be malignant, has returned, either in the same place or elsewhere, and has then undergone spontaneous cure. Some examples of such sequences of events are furnished by Sir Wm. Bennett.* In one case a foot was amputated for melanotic sarcoma; numbers of secondary nodules of typical round-celled sarcoma without pigment then appeared in the thigh, and the glands in Scarpa's triangle became enlarged. The prospects were regarded as hopeless, but six months afterwards the patient was in excellent health, the nodules had almost gone, and ultimately they vanished altogether. The other case is similar to this in almost every respect; and two others are described, in each of which a sarcoma of the scrotum or testis completely disappeared after being tapped. In one of these latter the disease was said to have existed for nine years, and to have been at a standstill for seven. This suggests that the tumour, though its microscopical characters were those of a sarcoma, was of intermediate or semi-malignant nature.

* 'Lancet,' 1899, vol. i, p. 3.

It is not possible to say whether in such instances as these recovery is due to the slight operation, or to the exposure to the air, or whether it is merely a coincidence. Probably instances of the spontaneous disappearance of tumours regarded as cancers are not nearly so uncommon as is supposed, seeing that the melting away of a cancer would usually be regarded as very convincing evidence that it is not a cancer.

It is by no means improbable that in the few cases which are published of disappearance after exploratory operations the absorption of the cancer was not solely due to the operation, but the operation happened to coincide with the rise of one of the aforesaid tides of improvement, and perhaps accelerated it.

Prognosis; Treatment.

There is probably no disease more dreaded than cancer, and for this apprehension there are two reasons. One is that it is to all intents and purposes a parasite; the other reason is the helplessness with which the existence of a cancer is usually regarded. Indeed, the very name is to most people tantamount to a sentence of death. Yet we know that this hopeless attitude is born of old-time ignorance, and is by no means justified by facts, for there is evidence that a good percentage of cancers are cured by prompt and vigorous treatment. One of these reasons for pessimism has its source in the multitude of remedies which have been advocated for its treatment, for the instinct of the people sees the weakness which underlies this situation, and appreciates the logic of the dictum that "the disease which has many cures has no cure."

Probably the chief excuse for this multiplicity of remedies is to be found in the irregularities which so often mark the progress of the disease. Any drug which happens to be used during one of the periods of reaction is pretty sure to be credited with the improvement. If the patient should happen to be a village washerwoman very little harm is done, for it is not likely that anyone will give more than a passing thought to her experience. But should the patient be a well-known society lady, the result is that a new "cure" is said to be discovered, or an old one resuscitated, and many an unfortunate victim, instead of going to the surgeon to receive the benefit of the best means of cure, flies to the new treatment, and is doomed. It is in this way that such popular remedies as violet leaves have got their fame, and that charlatans, like the notorious Mattei, have become so popular.

Of the methods of treatment which can be said to have a scientific basis some half-a-dozen deserve attention, not only for their own sakes, but because they help to establish the position of the malignant disease group. Of these by far the most adequate and successful is the first.

1. *Excision.*—All that is known on the subject of cancer tends to prove that it is a local disease, and that no method of cure is so sure as that of cutting it out, provided the malady be taken at such an early stage as to admit of its complete removal. And the evidence at our disposal goes to prove that recurrence is always due to some of the cancer-cells having been left behind. Mr. Mayo Robson, in the Bradshaw Lectures* for 1904, showed that the prospects of the patient who has been operated upon for cancer are far brighter than was previously supposed. The gist of his remarks is as follows: The prognosis after attempts at complete extirpation of cancer, still at a stage favourable for operation, necessarily varies with the operator and the part affected. The site most favourable to a radical cure appears to be the lip, an analysis of 114 cases of epithelioma from the Göttingen Clinic showing that 53 per cent. were alive and well or had died of other diseases more than three years after removal. In the figures of the Tübingen Hospital, analysed by Dr. Loos, there was the slightly higher rate of recurrence of 51 per cent. within three years' limit. But the influence of better methods of operating is indicated by the fact that this percentage of recoveries was increased in the years from 1885 to 1898 to 66 per cent. Mr. Robson then goes on to show that cancer of the tongue has a heavier rate of recurrence, amounting to nearly 160 out of 199 cases recorded by Butlin, Krönlein, Kocher, and Whitehead, or close upon 80 per cent., within the three-year limit. This mortality of 80 per cent., though far higher than that of cancer from other parts of the body, must be regarded as decidedly encouraging when we think of the nature of the organ concerned, of its abundant supply of lymphatics, and of the impossibility of cutting wide of the disease. Indeed, with such comparatively good results under such adverse circumstances the percentage of recurrence of cancer of the breast is high when we consider how great an amount of tissue may be removed, and how easy it is to get at the lymph glands which are most often implicated. American figures, collected by Professor Rodman, show that out of 629 cases operated upon by American surgeons 44·16 per cent. survived the three-year limit. But when we inquire a little further into these

* 'Brit. Med. Journ.,' 1904, vol. ii, p. 1501.

statistics the personal influence of the operator soon becomes evident, for Prof. Halstead's figures are decidedly better, amounting to 51·5 per cent. out of a list of 161 patients, and in England Mr. Mitchell Banks has had still better results, for out of 108 cases no less than 73·67 per cent. lived for three years or more without recurrence.

In regard to cancer in general Dr. Dollinger* traced out the after-history of 150 of his patients operated on by modern methods, and found that 40 per cent. were free from recurrence after the lapse of three years, and 41·25 per cent. (some were operated upon more than once) after five years.

Such figures as these tend to prove that cancer is a local disease, and that the question of cure depends upon the completeness of its removal. At the same time it is necessary to point out that statistics are often misleading, and that the three years' limit is undoubtedly too narrow, for recurrence sometimes takes place after six or even more years have gone by.

II. Inoculation with bacterial toxins.—It is conceivable that the improvement or cure which follows upon the exposure of a deep-seated cancer and upon incomplete operation is due to the attacks of bacteria to which the neoplasm is now for the first time exposed. There are many reasons for thinking that this may be the explanation.

(1) Cancer-cells, in common with other degenerated cells, have little vitality. Their nutrition is low, so that they readily succumb to the attacks of invading micro-organisms. Even in places seenre from these attacks their cells are often seen to be undergoing decay, not only in the middle, but also on the outskirts of cancer masses, and where there is no perceptible constriction. It seems pretty evident that if the external micro-organisms, or their toxins, can penetrate into the depths of such tissue, they may be quite capable of checking the progress of the cancer, or even of stopping it completely.

(2) It has been observed that cancers destroyed with caustics are sometimes apparently less prone to grow again than are those which are cut away. A good example of this may be found in the case of large inoperable sarcoma of the neck, published by Mr. Bowreman Jessett.† Here a tumour was almost cured by caustics, though other cancers of the same sort have shown themselves to be intensely malignant, speedily returning after removal

* 'Deutsche medicinische Wochenschrift,' 1905, Bd. xxi, S. 1461.

† 'Illustrated Medical News,' 1888, vol. i, p. 135.

with the knife. This result may possibly be due to the fact that an ulcer had been made, and that into this ulcer all sorts of micro-organisms gained entrance, and, by means of their toxins, acted upon any cancer-cells which may have been left behind.

(3) Cancers on the surface of the body, which have ulcerated or are accessible to the air, are as a rule of slower growth, and are less malignant than those which are deep-seated. The epitheliomata are as a class among the least malignant of all cancers. Generally speaking, ulcerating cancers of the rectum, of the vulva, of the lips, and all rodent ulcers, are of slow growth, and may be eradicated at a later date and with less sacrifice of tissue than other forms of cancer. Carcinoma of the cervix uteri is, it is true, more malignant, and, indeed, disseminates so readily into the abundant lymphatics of the part that it can seldom be extirpated, even by complete removal of the organ in which it grows. But one of the chief reasons for this apparent exception is that owing to the only occasional use of the uterus, to the insensitiveness of the cervix, and to its sheltered position, a cancer of that part has generally made considerable headway before it is discovered.

The tissues round about a cancer of the rectum occasionally inflame and break down into abscesses. It has been noticed at times that after such abscesses have discharged the cancer has undergone decided improvement. It may give very little trouble for many months afterwards or even disappear altogether.* The same happy ending has been noticed when other cancers have suppurated. Thus in a case reported by Dr. Richardson, a large infiltrating round-celled sarcoma of the axilla and neck almost disappeared after suppuration had taken place.

(4) Similar results have been observed when a patient suffering from cancer has become accidentally infected with erysipelas. It has occasionally happened that the cancer, especially if it be a sarcoma, has diminished in size or disappeared. This fact has been utilised by Dr. Coley, who has introduced the method of treating cancer by means of the mixed serums of *Bacillus prodigiosus* and *Bacillus erysipelatosus*. A similar plan was once adopted by Emmerich after an abandoned operation for the removal of a cancer,† in which case the patient died suddenly two years after the operation, with evidence of mediastinal metastasis. Though the trial of this method has been amply justified by the observations upon which it was founded, and by its results, it has perhaps

* Dr. H. J. Cotton, 'Trans. Roy. Med. and Chirurg. Soc.,' 1904, p. 627.

† 'Annals of Surgery,' 1904, p. 741.

done most good by strengthening the opinion of those who hold that no method of treatment can approach that of free excision for safety, mercy, and efficiency. Inoculation has a disintegrating effect upon the cancer, bringing about fatty degeneration of its cells, and promoting infiltration with leucocytes, such as occurs in spontaneous recovery. But the method is, in the hands of some investigators,* attended with all the dangers, discomfort, or misery of repeated bouts of severe illness. This, however, is not the experience of Dr. Coley himself, who has met with most encouraging success in the cases which have been submitted to him for treatment.†

Dr. Coley brought this subject before the Royal Society of Medicine in 1909,‡ and in a convincing paper showed that he had to all appearance cured no less than fifty-two cases of cancer, and could find twice that number successfully treated by others. It is not easy to make out from his paper what is his percentage of recoveries, but one gathers from one paragraph, in which, referring to the death-rates, he says, "In my own experience in nearly 500 cases there have only been three deaths," that his successes amount to a little over 10 per cent.

Something analogous apparently takes place when a growth is subjected to the action of *X rays* or to *radium rays*. There is no reason to suppose that these penetrating rays exert any specific action on malignant cells. They act exactly as they do upon healthy tissue. If applied for a sufficient time or to a sufficient degree they are capable of destroying the cells of the normal skin. Used to a less degree they are capable of slowly destroying the cells of the cancer which lies beneath them, without producing any eczematous eruption of the skin itself.

The *rationale* of this plan of treatment seems to consist in bringing a devitalising or disintegrating influence to bear upon cells whose resisting power is lower than that of the tissues in which they live; but this subject will be referred to in more detail later on.

That such treatment by means of X rays is sometimes successful has now been proved by the publication of successful cases, but generally speaking, though it sometimes delays the progress of the malady, its effects are variable and disappointing. The depth to

* See Kopfstein, 'Wiener klinische Rundschau,' Nos. 33 and 34, 1895.

† 'Amer. Journ. Med. Sci.,' 1906, N.S., vol. cxxxi, p. 375. See also supplement to the 'Twentieth Century Encyclopædia of Medicine,' p. 759.

‡ 'Proceedings of the Royal Soc. of Med.,' vol. iii, No. 1.

which the rays penetrate is said to be slight, and they are most successful when they produce necrosis.* Short of actual death of tissue the changes effected resembled those which occur in ordinary fibrous degeneration. A case has been published by Dr. Cleveland and Mr. Davy† in which an advanced cancer of the uterus, the nature of which was verified during an unsuccessful attempt to remove it, entirely disappeared after the application of X rays. This example is the more conclusive in that ten weeks elapsed after the operation before improvement set in, and a temporary cessation of treatment was followed by a return of symptoms.

Such cases as this, and also that published by Mr. Marmaduke Shield,‡ show that it is not yet time to despair of the treatment of severe inoperable cases of cancer with X rays.§ When malignant disease is superficial the X rays almost always relieve pain, retard growth, produce molecular degeneration, and may enable patients to resume their ordinary life; but if the cancer affect the viscera it is impossible to modify it without injuring the skin. Dr. Bill,|| in writing on the use of X rays in malignant disease of the orbit, inoperable or recurrent, refers to the relief from pain which is gained by the treatment, and says that out of ten cases which have come under his observation, two were so much improved that they seemed to be cured, but that in eight cases of sarcoma no good resulted.

The best results have been obtained with such superficial cancers as rodent ulcers, epitheliomata of the palate, lip, anus, and vulva. Melanotic sarcoma has also been treated with success; but, so far, the treatment of carcinomata of the breast and other parts has not given much satisfaction, and there has often been the serious drawback that tiresome and painful inflammation or ulceration has been produced without any compensating advantage.

According to the experience of the Imperial Cancer Research investigators, *radium* causes some cancers to disappear, but does not act in a uniform manner under similar circumstances. It is believed that there is some state of the cells which modifies the result. If, in the course of the cyclical changes which are inherent in malignant tissue, the radium happen to be used at the period of recession, it would intensify that period and carry it on until the cancer vanishes.

* 'Third Report of the Croft Cancer Commission,' article by Drs. Vose and Howe, p. 59.

† 'Brit. Med. Journ.,' 1905, vol. i, p. 925.

‡ 'Lancet,' 1905, vol. ii, p. 1464.

§ Lyster, 'Archives of the Middlesex Hospital,' vol. v, 1905; 'Brit. Med. Journ.,' 1905, vol. i, p. 1278.

|| 'Brit. Med. Journ.,' 1905.

Hence, "the processes directly concerned are parallel to those observed when a new growth undergoes spontaneous absorption." And we have already noticed that the same may be said of treatment with X rays and with toxins.

The effect of radium is apparently to modify the nature of the degeneration, for the result of its action closely resembles an inflammatory reaction with exaggerated repair. There is marked proliferation of the surrounding connective tissue, and, about twelve to fourteen days after exposure the parenchyma cells become vacuolated, and are afterwards absorbed.*

Professor Einhorn† has used radium for cancer of the gullet with encouraging results. Of nine patients upon whom this treatment was tried, in six the cancer seems to have receded, for the strictures were widened, but no good seems to have resulted from its application in the other three.

As to the *rationale of the treatment by means of X rays and radium rays* opinion is, of course, divided. Some authorities believe that they exert a direct action on the cancer-cells, while others, and among them Dr. Bashford, hold that the action is indirect, and that molecular degeneration of the malignant cells is the result of proliferative changes in the surrounding meshwork of connective tissue. But having in view the direct action of a decomposing nature which radium is known to exert on nuclein, one may perhaps venture to ask whether the vacuolation and other changes in the cancer-cell are not produced in a similar way.

Birch-Hirschfeld‡ says that radium acts on all cells and that the chromatin suffers, while growth is retarded and the cell becomes deformed. Some cells are more susceptible than others, those of a cancer being much more deeply affected than are the normal cells around it. It seems clear that these rays reduce the activity (malignancy) of the degenerative process and tend to change it from the single cell type to one which more nearly resembles that characteristic of fibrosis in organs.

It was apparently first shown by Drs. Tilden Brown and Osgood§ that men engaged in X-ray work are liable to become

* Scientific reports on the investigations of the Imperial Cancer Research Fund, under the direction of the Royal College of Physicians of London and the Royal College of Surgeons of England. By Dr. E. F. Bashford, No. 2, Part II. "The Growth of Cancer under Natural and Experimental Conditions."

† 'Journ. Amer. Med. Assoc.,' vol. xlv, 1905, p. 8.

‡ "Proceedings of Fifteenth International Medical Congress," 'Lancet,' 1906, vol. i, p. 1286.

§ 'Archives of Röntgen Rays,' March, 1905.

sterile from the non-secretion of seminal fluid. Margaret Cleaves* then published a case in which temporary aspermia resulted from the treatment of pruritus ani with X rays and lasted for about three months. Miss Cleaves found that this experience was in accordance with the observations of Drs. Albers-Schönberg† and Friebe,‡ who had noticed that the seminal epithelium of rabbits was destroyed by X rays, and with those of Halberstaedter,§ who had seen similar changes in their ovaries.

These facts apparently show that the special cells of the testes or ovaries are, like cancer-cells, more affected by the X rays than are the cells of the skin and other more superficial structures.

Radium gives off three forms of rays— α , β , and δ . The first consist of positively charged particles of little penetrating power; the β rays resemble the cathode rays of Crooks's tube, are negatively charged, and are penetrating and powerfully actinic; the δ rays are still more penetrative, and resemble the Röntgen rays from a hard tube.||

A trial of *thorium* rays has been advocated by some writers, though they are about a million times weaker than radium rays. The hydroxide of thorium is said to be cheap, and could be used in large quantities enclosed in a rubber bag.¶

III. Arsenic.—The only exception to the rule that cancer is incurable by drugs seems to be furnished by arsenic. The use of this drug in the treatment of cancer dates back to the time of Hippocrates, and instances of its value are still recorded. Thus Dr. O. Lassar** has published an account of four cases of carcinoma which entirely disappeared during internal treatment with arsenic, and Mr. Golding Bird†† a case of sarcoma which was apparently cured by the same drug. Dr. Jackson, of New York, has also recorded an instance of idiopathic, multiple, pigmented sarcoma (Kaposi type) ‡‡ which underwent decided improvement when treated with arsenic. Dr. Morris Hyde met with even greater success in a similar case, also treated with large doses of arsenic, though he denied that the disease was true sarcoma, notwithstanding that

* 'Medical Electrology and Radiology,' 1905, vol. vi, p. 65.

† 'Zeitsch. f. ärzb. Fortbild.,' Jena, 1904, Bd. i, S. 37.

‡ 'Münch. med. Wochenschr.,' 1903, Bd. i, S. 2295.

§ 'Berlin. klin. Wochenschr.,' Bd. xlii, 1905, S. 64.

|| Dr. Dawson Turner, 'Brit. Med. Journ.,' 1903, vol. ii, p. 1524.

¶ Dr. Davidson, 'Brit. Med. Journ.,' 1904, vol. ii, p. 181.

** 'Berlin. klin. Wochenschr.,' Bd. xxxviii, 1901, p. 249.

†† 'Clinical Society's Transactions' (unverified).

‡‡ 'Brit. Med. Journ.,' 1897, vol. ii, p. 867.

the histological features were distinctly those of spindle-celled sarcoma.

Though these and many other instances* have been published from time to time, yet it cannot be said that the efficiency of arsenic has been established.

One can only say that there is apparently more evidence in its favour than there is for any other drug, and that it ought to be given in every case of cancer, whether operated upon or not.

General Therapeutics.

There is a general impression, which is shared by clinical observers of great acumen and ability, that malignant disease is in part the result of insanitary or otherwise depressing conditions of life. There is also reason to believe that it is less common among those living a free, open-air, unrestrained existence, such as most savages and semi-savages live, than among those used to the luxuries and attendant cares and conventions of civilisation. At first these two opinions seem to neutralise one another, for we none of us look upon the life of the savage as either sanitary or care-free, though it is certainly *careless* when compared with the life of the average civilised man. In the absence of discriminating statistics it seems impossible to come to any conclusion on this subject.

The treatment of inoperable cancer of the breast in women by removal of the *ovaries*, advocated by Beatson, has been carried out by Mr. Stanley Boyd, Mr. Lockwood, Dr. Herman and many other surgeons. Of the published cases the result has been only fairly satisfactory, and it may be safely conjectured that many of the least successful cases have never been recorded.† Mr. Stanley Boyd,‡ who has taken great interest in this method of treatment, and collected statistics on the subject, showed that in nearly 6 per cent. the cancer became either stationary or actually disappeared, and had not recurred for a period of two years and over. He regards the operation as most effective in the less rapid cases in women over forty, before the onset of the menopause, and in whom there are no secondary deposits. It is usually thought that the results are due to the interference with some secretion which is

* See Dr. Tilley's case of sarcoma of tonsil, Brit. Med. Journ., 1904, vol. ii, p. 1642.

† We have tried this method in one case—unsuccessfully—and have not published it.

‡ 'Brit. Med. Journ.,' 1900, vol. ii, p. 1161.

normally poured out by the ovaries, but in what way this secretion acts or why its removal should inhibit the growth of cancer of the breast, and no other part, is not very clearly explained. It seems much more likely that the effect is due to the action of that physiological sympathy which exists between the ovaries and the breasts, such as is ordinarily seen in the rapid growth of the breasts when the ovaries ripen at puberty, and in the shrinking of the breasts when the ovaries degenerate. A similar effect is also to be witnessed in the degeneration of the bone-marrow of osteo-malacia, when shrinkage and return to the normal takes place as the result of the removal of the ovaries. In explaining such occurrences as these it is not necessary to assume the intermediation of any secretion. Everything can be accounted for by the correlation naturally existing between these organs, similar to that which occurs between the growth of muscles and of the skeleton, and between other physiologically related parts which possess no secretion.

Castration tends to hasten the degeneration of the breast. But we have already seen that the malignancy of cancer is greater in young tissue than it is in senile tissue. Hence, anything which will accentuate the senility of a cancerous organ must indirectly lessen the malignancy of the cancer.

VI

RELATIONS OF THE CANCER PROCESS TO ALLIED CONDITIONS

Pre-natal malformations, innocent tumours, degenerations of organs, and normal old age, prepare the way for cancer formation. Among pre-natal malformations are cell rests, which are cells in a state of infantilism. New growths predispose to cancer degeneration because their cells are already slightly degenerated; and the same is true of degenerated organs and of normal senility. The embryonic cells of a cancer are so alien to the part they affect that, like a foreign body, they provoke an irruption of phagocytes, leading to the formation of fibrous septa and of a spurious capsule. Cancer may in this way be the starting-point and focus of degeneration of an entire organ. The common factor in all the above associated conditions is either infantilism, or degeneration, in the first place, and in the next a lack of sympathy between the degenerated part and its surroundings.

CANCER has intimate relations with (1) pre-natal malformations, (2) innocent tumours, (3) the degenerations of organs, and (4) normal old age.

Pre-natal malformations.—There is plenty of evidence that cancer is peculiarly prone to affect those organs or parts which are not of normal growth or development, no matter whether the imperfection be one of defect or excess. For example, a breast which has not developed, especially if it be also misplaced, is very apt to become the seat of cancer, and the same may be said of the testes.*

Dr. Max Borst,† in referring to the association of these morbid conditions, gives a number of examples and brings out very clearly the fact that it is not only the undeveloped organ which shows this feature but also that which is overgrown. This is particularly true of the reproductive organs and their satellites.

Instances are on record of cancer of the uterus‡ in combination with arrest of growth or development of the sex organs, and it is well known that those who are afflicted with premature development

* Mr. Bland-Sutton, 'Practitioner,' 1910, vol. lxxxiv, p. 27.

† 'Die Lehre von den Geschwülsten,' Bd. i, S. 88.

‡ See Danel, 'Journ. de la Soc. Méd. de Lille,' January 21st, 1905.

of these same organs are also liable to cancer. Out of sixty-nine instances of sexual precocity in girls collected by Dr. Williams* no less than thirteen were affected with intra-abdominal tumours, ten of which were sarcomata and two cystomata, eleven being ovarian and two (sarcomata) adrenal.

Ploss† found three instances of ovarian tumours among sixty-two cases, and Riedl‡ has recorded another in which sarcoma of the left ovary manifested its presence in a child of six more than two years after the onset of precocious puberty.

In some of these instances the sarcoma is supposed to have occurred first and to have induced the sexual prematurity, and in those cases in which the tumour was taken away the precocity ceased, but as a matter of fact the tumour is not cut away from the ovary, but both tumour and ovary are removed together so that the good accomplished may be the result of the reduction of ovarian activity rather than the loss of the tumour.

One fact of great importance in its bearing upon our subject is that cancer not only occurs when entire organs are affected with some malformation, but also when only a few cells of an organ are at fault. It is notorious that cancer is prone to arise where cells are cut off from their natural relations, and are isolated as “rests” away from their own peculiar organs.

We must also include among cell rests those cell inclusions which give rise to *chorion-epitheliomata*. This kind of cancer in its most characteristic form springs from the inclusion within the uterus of the mother of certain cells which belong neither to her nor to the child, but are for temporary use only, being ordinarily cast off so soon as they are done with—that is, at the birth of the child. Such cells are essentially of a low order of development, for they are thrown out from the blastoderm at a very early stage; and, acting merely as a go-between, it is not necessary for them to make any real progress beyond their primitive state. It is these cells, when left behind and imbedded in the far more highly developed tissue of the uterus, that are so prone to become malignant. These statements also apply in effect to those cancers which arise from the same or analogous tissue existing in teratomata.

It has long been held that some benign growths are peculiarly liable to undergo transformation into cancer. This view is held, among others, by Sir James Paget, Sir Jonathan Hutchinson, and

* ‘Brit. Gynæcol. Journ.,’ May, 1902, p. 85.

† ‘Das Weib in der Natur- und Völkerkunde.’

‡ “Menstruatio præcox und Ovarialsarcom,” ‘Wiener. klin. Wochenschr.,’ 1904, Bd. xli, S. 942.

Dr. Max Borst. The innocent tumours which are regarded as most likely to undergo this change are sebaceous adenomata, moles, warts, and adenomata in general, but no innocent tumour seems to be more liable to undergo cancer degeneration than the multiple polypoid adenoma of the rectum. Mr. Childe, of Portsmouth, who has described an instance of the occurrence of the cancerous transformation of this disease in three sisters,* mentions a similar sequence in another family and alludes to other cases. Another good example is described by Messrs. Lawford Knaggs and O. P. Gruner.

In these instances the ages and sexes of the patients, the fact of heredity and the structural relations of the cancers to the innocent tumours all point to the transformation of the one into the other.

Among the new growths which are known to undergo malignant transformation are the fibromyomata. Though it is denied that this change ever takes place, examples have been recorded by Dr. Horrocks, Mr. Alban Doran, Dr. Cameron, of Glasgow, and other authorities. Dr. Haultain believes that all encapsulated sarcomata of the uterus are derived from fibromyomata,† and Dr. Mesko-Stroganowa‡ gives details of the examination of a series of twelve cases. She recognises two forms of malignant transformation, to wit, myoma malignum and leiomyoma malignum. The former is ordinary sarcoma and is intensely malignant. In the latter, which is less malignant, cells resembling or consisting of unstriped muscle compose the greater part of the tumour.

Relation of cancer to the degenerations of organs.—It is an item of general medical knowledge that any organ which is the seat of fibrous or other form of integral degeneration is more prone to become the seat of cancer than is one which is healthy. In the case of some organs the more generalised degeneration so often precedes the more local change that it is a moot point whether the former should not be regarded as necessarily a pre-cancerous condition, and should be extirpated before the cancer has had time to appear. It ought particularly to be noticed that, as a rule, it is the less diffuse forms of generalised hyperplasia which are most liable to become the seat of malignant change. Thus, the very diffuse degeneration of the liver of ordinary cirrhosis is but rarely the starting-point of cancer, whereas the more local degeneration of the epithelium of the lip or tongue, termed ichthyosis, is probably more frequently associated with cancer formation than is any hyper-

* 'Brit. Med. Journ.,' 1905, vol. ii, p. 805.

† Profs. Allbutt and Playfair's 'System of Gynæcology,' p. 586.

‡ 'Monats. für Geburts. und Gynäk.,' September, 1903 ('Brit. Med. Journ.,' "Epitome").

plasia of an entire organ. So also in Paget's disease of the nipple the occurrence of a patch of "eczema" about that part in middle-aged women who have suckled children is so often followed by the appearance of cancer that same authorities have regarded the so-called eczema as a cancerous change from the beginning, though this view has now been proved incorrect.

One reason why it is in some instances difficult to make sure whether the cancer comes first in order of precedence is that degeneration starting in cells seems to infect the surrounding healthy cells, so that they, too, undergo degeneration. But this secondary degeneration is at first of that less violent character which is, as we have already seen, associated with degeneration of organs. On examination of the growing edge of a cancer we observe that it does not cease abruptly, as if pushing aside a well-defined line of normal tissue, but merges into the healthy structures by degrees. The intermediate tissue consists of those round cells which are regarded as evidences of resistance to the cancer on the part of somatic cells, such as occurs when a foreign body is present. Now, there is much difference of opinion as to what really takes place round the margin of original cancers. Dr. Max Borst, Dr. Rolleston and others are positive that there is no transformation of normal into cancer-cells. But other observers are quite as emphatic in declaring that such transformation undoubtedly takes place.

Professors Farmer, Moore and Walker* assert that on the outskirts of a *primary* cancer may be seen all stages of transformation from normal gland-cells to cancer-cells. They also state that within the outer zone of such a tumour there is a crowding of leucocytes, some of which may be seen lying within the cytoplasm of adjacent cancer-cells—a phenomenon which they say does not occur in ordinary inflammation. But, strangely enough, neither the leucocyte nor the invaded cancer-cell appears to be altered by this inclusion. Moreover, in many instances it has been found that while the cancer-cell is dividing mitotically, the enclosed leucocyte is going through similar divisions. "Both nuclei either pass through their pro-phase evolutions upon separate spindles or the spindle figures become confused, as is ordinarily the case in the first division of the ovum."

Klebs,† who had already described this position of the leucocyte in relation to the cancer-cells, believes that the invading leucocytes act the part of sperm-cells. Whatever the explanation may be, it

* 'Lancet,' 1903, vol. ii, p. 352.

† 'Allgemeine Pathologie,' Bd. ii, S. 524.

seems clear that leucocytes behave as intermediaries between the cancer-cells on the one hand and normal epithelial cells on the other.

This may be one way in which the gulf separating cancer from gland-cells is bridged, but there is possibly another way.

It is possible that at times the specific cells of an organ are first reduced to some lower state and afterwards degenerate to the last degree into cancer elements. Such, at any rate, appears to be the sequence of events when a fibrous organ becomes widely malignant. As a matter of fact there can be observed in all primary cancers three distinct stages of devolution. As the cancer-cells push their way into the substance of an organ they excite proliferation of connective-tissue cells. The connective tissue so formed constitutes a meshwork of alveoli, by which the cancer-cells are enclosed, and the more chronic the cancer the more abundant the fibrous tissue. Now it is essentially the epithelioid cells, and not the fibrous tissue, which constitute the cancer. Hence every cancer area consists of (1) cancer-cells; (2) fibrous tissue, formed, or in process of formation, representing an intermediate stage; and (3) cells at the periphery, which are normal to the part affected. In terming the fibrous meshwork "intermediate," it is not meant, of course, that it degenerates into cancer, but that it is neither normal tissue nor malignant, but is degenerative, and takes a position in the stage of development somewhere between the two.

That it is intermediate is pretty conclusively proved by the way in which it occasionally passes on into cancer. As a rare event the fibrous septa become sarcomatous (see p. 157), and so overwhelm the epithelial elements which they encase that at last a tumour which began as a carcinoma ends as a sarcoma.

The fibrous hyperplasia appears to be the outcome of an attempt on the part of the surrounding tissues to adapt themselves to the lower organisation of the cancer. Evidently the wider the developmental gap which separates the cancer from its surroundings, the more difficult it must be for this adaptation to take place. Its amount consequently bears an inverse relation to the degree of malignancy, for the more intense the malignancy the less the connective tissue. Moreover, it will be more readily formed by tissues which are already senile than by those which are still juvenile. The genesis of these fibrous septa seems to be as follows: So soon as cells revert to an embryonic state they cease to be in harmony with the normal tissues of the body. In other words, they virtually become foreign substances, and stimulate into activity that department of the body whose office it is to deal with the milder forms of invasion. Phago-

cytes appear on the scene, chief among them being the connective-tissue corpuscles. These proliferate, make unavailing attempts to cope with the cells of foreign aspect, and subsequently again pass into their resting state as the inert constituent of new bands of fibrous tissue. But owing to the fact that they have undergone multiplication, and perhaps also to their being supplemented by other sorts of phagocytes, the amount of fibrous tissue is far greater in the end than it was in the beginning.

Of all the characters of cancer its power of unceasing proliferation is one of the most distinctive, serving to distinguish it from all purely innocent growths. Continuous cell multiplication, however, does not distinguish malignant degeneration from the degeneration characteristic of organs. Such a process as that which gives rise to cirrhosis of the liver, primary splenomegaly, or osteomalacia is, in fact, not innocent at all, but semi-malignant. It has hitherto been thought that the circumstance which is most significant of malignancy is the dissemination of the disease to distant parts. But the tendency is now to think less of this sign and to minimise its frequency. Mr. W. S. Handley,* after careful investigation of the spread of carcinoma of the breast, came to the conclusion that it spreads centrifugally, independently of the flow of lymph or blood, and is often in continuity throughout. The disease apparently pushes its way along the lymph channels and invades liver, bone, and other tissues in order of sequence. But even when cells become detached this does not greatly affect our argument, for it has been shown by Ehrlich, Banti and others that there is just as true metastatic or embolic dissemination going on in leukaemia as there is in any cancer. Moreover, the disease process in some degenerated organs is just as inveterate and pernicious as it is in cancer. Fibrosis in a cirrhotic liver does not come to an end while life continues, and the same may be said of proliferation of the marrow in pernicious anaemia and of bone in osteitis deformans. It is true that in the degenerating organ the morbid process is, as a rule, shut up within the compass of the affected organ. Nevertheless this is not a vital distinction—the result of a radical difference between the two processes. It is due to the fact that one happens to affect cells which are ripe for reversal of their development, even to the degree of modified unicellular independence, while the other affects cells which, for an untold number of generations, have been accustomed to all the restraints which are implied in the word “organ,” and are still bound by this tradition, even when they undergo a process of reversion.

* ‘Archives of the Middlesex Hospital,’ vol. iii, 1903.

Malignant degeneration of cells, therefore, comes into relation with the more widespread degeneration of the entire organ in two directions. Sometimes the degeneration of the organ as a whole precedes the single cell degeneration, and is its immediate cause; at other times the degeneration of the single cell is the precursor and originator of the degeneration of the organ. Sometimes the one is the parent and the other the offspring, and sometimes the order is reversed. These dual and interchanging relations are well exemplified in the case of the liver. As a rule it is the cirrhosis of the liver which comes first, and the malignant disease which follows, but in the opinion of Max Borst,* among others, there may be widespread carcinomatosis of the liver, which simulates cirrhosis by causing the formation of quantities of interlobular fibrous tissue. In some of these mixed cases it is impossible to say which is antecedent—the malignant degeneration of the cells or the fibrous degeneration of the organ. But it is interesting to note that the widespread carcinomatosis now referred to behaves differently from the ordinary nodular carcinoma of the liver. It remains diffuse, does not extend to other organs, and acts quite as much like a fibrous degeneration as like a cancer. It is, in short, only locally malignant, and is apparently a compromise between the two forms of degeneration—that of cells and of organs. Similar compromises take place in the bone-marrow, where it may be difficult to decide whether in a certain case we have to do with an endosteal sarcoma, a myeloma, or osteomalacia.

The bearings of normal old age on malignancy will be referred to at a later stage.

The Common Factor in Pre-natal Malformations, Innocent Tumours, Cancers, Degeneration of Organs, and Senile Decay.

The nature of the relations that exist between cancer, on the one hand, and the malformations, innocent tumours, and degenerated organs on the other, is evidently one of cause and effect. But what is there about these latter morbid conditions which renders them liable to undergo cancerous degeneration? The answer to this question is only to be found by seeking for some factor common to all. Now if we examine these different conditions we notice that every one of them consists in a deviation from normal growth or development. In each case the tissue at fault is out of sympathy

* 'Die Lehre von den Geschwülsten,' Bd. ii, S. 566. See also Ziegler, 'Lehrbuch der Speciellen Patholog. Anat.,' Bd. ii, S. 644.

with its environment. It either lags behind, as in the pre-natal defects, or goes too far ahead, as in the growth excesses, or in the premature degenerations of organs. The same process is at work in the cancer as is in action in pre-cancerous conditions, but there is either a change from a more passive (*i. e.* growth) to a more active (*i. e.* developmental) process, or the degeneration is not spread equally over the entire organ, but is focussed on to one group of cells.

That this is the right explanation is proved by the circumstance that wherever cells in the course of development are cut off from their natural surroundings they are liable to become cancerous. They are not in touch with the cells of the tissue in which they lie, and therefore develop along a line of their own, uninfluenced by their environment. But it is probably not enough that they should be merely present—no more enough than that there should be gun-powder in order to produce an explosion. Some friction or other irritation is necessary to start the dormant cells into activity, though in many cases what that stimulus is is so occult as to be beyond our knowledge. It seems clear that cancer does not often spring straight out of normal cells. There is, as a rule, and perhaps always, an intermediate stage. This consists either in retarded development of cells, or in their premature reversion or degeneration. In one word, cells must become *quasi-embryonic* before they can start on that process of proliferation which we term “cancerous.” This malignant regression is, as we have just said, peculiarly liable to set in when small collections of cells are, from any cause, not in harmony with their surroundings. Thus some cancers of the liver, of the kidney, and of the reproductive organs, are due to the degeneration of adrenal cells, which have in the course of development become detached from their natural position and remain embedded in the alien organ, and one may speak in a similar way of aberrant thyroids, testes, and breasts.

But there is another way in which cells may become isolated and made to take up a position of non-conformity with their fellows. Ribbert holds that in cancer formation there is always an isolation of differentiated cells of the nature of “post-natal rests.” He believes that in all cases the cells of a cancer have arisen from cells which are not normal to the part, but have undergone some change — lupoid, syphilitic, fibrous, adenomatous — of a degenerative character, which has caused them to assume the attitude of strangers. These post-natal rests differ only from pre-natal rests in that they are not pioneer or progressive cells which have been cut off from

their main body, but cells which have been made to assume a similar isolated position by a reversion of development. In the one case the cell rests are isolated from the beginning, in the other they become rests secondarily. The difference between them may be compared to the spume which is thrown forward by the advancing tide, on the one hand, and that left behind by the receding tide on the other.

VII

STRUCTURE AND PATHOLOGY OF CANCER; CARCINOMATOSIS; MULTIPLE CANCERS; RELATION TO OLD AGE

Though essentially a senilism of single cells, cancer may be widespread (carcinomatosis, sarcomatosis), or occur simultaneously in widely separate organs. Certain nuclear changes indicative of extraordinary proliferative activity have been noticed in cancers, reproductive cells, and leucocytes. Cancer is not due to the immediate multiplication of cells of defective development. The cells undergo the reversible changes of declining development first, and the cancer is an indication of senility (second embryonic life), not of a re-awakened dormant first embryonic life. Reversion is not complete, for cancer-cells still partake of the nature of the tissue or organ from whence they come. Cancer has peculiarly close affinities with the generalised old age process.

Nothing apparently is more certain than that cancers are not due to any generalised infection, but are local disturbances. Certain facts which seem to point to a more widespread origin can readily be accounted for on other grounds.

(1) One of these is that cancer sometimes affects large tracts of tissue or even entire organs almost simultaneously. Perhaps the most striking instance of this occurs in the stomach. Cases have again and again been recorded of so-called fibrosis of the stomach, and it has been taken for granted that these are either non-malignant, or that the cancer, if manifestly present, is only part of the trouble, and is secondary to the fibrosis. But the investigations of Drs. Perry and Shaw* go to prove that this is a mistake, and that in all, or nearly all, there is a simultaneous, more or less generalised malignant degeneration. The liver or the gall-bladder also may be affected with similar generalised carcinomatosis.

(2) There are, further, a number of instances on record of the occurrence of primary cancer in both breasts, both retinae, both ovaries,† both parotids, both carotid bodies,‡ or in both adrenals.§

* 'Guy's Hosp. Reports,' 1891, vol. xlviii, p. 137.

† Dr. Cuthbert Lockyer, 'Brit. Med. Journ.,' 1904, vol. ii, p. 1430.

‡ H. Gilford and K. L. Hart-Davis, 'Practitioner,' 1904, vol. lxxiii, p. 729; also Dr. Barbour, Edinburgh Obstetrical Society, May 10th, 1905.

§ Dr. Woolley, 'Trans. Assoc. Amer. Physicians,' vol. xvii, 1902, p. 627.

(3) Sometimes the cancer occurs almost simultaneously in widely separated organs, under circumstances which indicate that one cancer is not the parent of the other. Dr. Richter, of Vienna,* has recorded some examples of this association. In one patient an adeno-carcinoma of the thyroid gland co-existed with an epithelioma of the uterus. In another there was an adeno-carcinoma of the breast and an epithelioma of the uterus, which were mingled together in the liver. The author gives, in addition, two cases of the occurrence of multiple primary carcinomata in different organs.

We have ourselves seen a patient with simultaneous carcinoma of the uterus and breast, and also an example of multiple primary cutaneous carcinomata. These latter broke out almost simultaneously in different parts of the body in an old lady, aged 82 years. There were at least thirteen of them scattered over the forehead, scalp, back, one leg, and the upper limbs. Next to their simultaneous appearance and their nature, their chief peculiarity was a strong tendency to bleed. When no bigger than pin-heads some of them bled profusely, and here and there, in addition to the thirteen superficial growths, were a few subcutaneous blood-cysts of small size, all probably cancerous. The lady died six weeks after their appearance as the result of old age accelerated by the cancers. A *post-mortem* examination was made by Dr. Sidney Gilford, who ascertained that there was no internal metastasis whatever. The tumours were not epitheliomata. There were no concentric groups, but cells of epithelial type were arranged in irregular, imperfect alveoli.

These two circumstances, to wit the occurrence of diffuse forms of cancer (carcinomatosis, sarcomatosis, etc.), and the simultaneous appearance of cancer in remote regions of the body, seem to point to the operation of a general cause. But in reality all that these facts indicate is that cancer does not start directly from vigorous young cells, but from cells whose development is on the wane. Hence organs which are undergoing the premature degeneration of senilism may be the starting-point of widespread carcinomatosis, the malignancy and senilism appearing almost at the same time. We know how usual it is for bilateral organs to degenerate together, and for more than one organ to fall into old age at the same time. And there is no reason why two widely separated parts of the body should not, by pure accident, be affected at the same time by a disease process which is comparatively common in old age.

* 'Wien. klin. Wochenschr.,' Bd. xviii, 1905, S. 865.

Structure.

A cancer diverges in structure from that of the organ from which it springs. This heteroplasty is shown by the more irregular distribution of its cells, by increase or decrease in size, by changes within the cells, and by alterations in the size and form of their nuclei. Many of the cells seem to reproduce themselves in the most primitive way by simple fission of their nuclei, without karyokinesis, while others are said to show a form of mitosis such as is seen in no other somatic cells. They also exhibit changes in the affinities of their protoplasm, and of their nuclei, for certain stains, different from those of their parent-tissues. It is not necessary to go into the details of all these various alterations. It is sufficient that they exist and serve to prove in a very emphatic manner the profound and far-reaching difference between cancer-cells, and the cells normal to the organ, or tissue in which they grow. But wide as this difference is, we must still recognise that the whole pathological process has a biological basis. We are evidently dealing with cells which belong to the body in which they are found, though they are of exceedingly low type. This is shown in the way in which each variety of cancer retains the marks of the tissue from which it originated, and passes them on to its offspring. They always "breed true." The sarcoma shows its connective-tissue origin, the carcinoma its epithelial, and so, in a similar way, with the endotheliomata and the chorio-epitheliomata. Of late much attention has been called to the fact that occasionally, when cancer-cells divide, the number and arrangement of the chromosomes seem to prove some affinity to reproductive tissues. In reality, however, all that can be said of this peculiarity is that it carries us back to a form of cell which corresponds in some respects with the primitive germ-cell. Such a parallel may mean no more than that some of the cells of cancer-tissue have so lost their identity as to become engrossed in proliferative changes to the complete extinction of all other functions. They become so degraded as to lose all functions except one, and that the most primitive of all. They are like criminals who have given up all legitimate work, and attained a vicious form of specialisation.

An important circumstance in connection with cancer is that no one has yet been able to trace its beginning. Consequently all views on the subject are more or less conjectural, for the evidence is of necessity circumstantial. All the theories which have been brought forward to explain its occurrence may be put into one of

two classes. It is attributed either to the almost sole action of some external cause, such as sporozoa, or bacteria, or to some internal change. These contentions, again, may be gathered into the fold of two theories, namely, the parasitic theory and the theory of embryonic rests, as originated by Durante,* elaborated by Cohnheim, and extended to post-embryonic conditions by Ribbert. The view of Durante and Cohnheim is that the initial factor of malignant disease is the presence of cells which have never got beyond an embryonic stage of development. It is supposed that these aberrant, resting elements, under the stimulus of some irritant, or spontaneously, resume their original activity, and, being entirely out of sympathy with the slow growing and mature cells among which they lie, proliferate rapidly, push aside adjacent tissues, and become piled up into heaps of embryonic or badly developed cells.

With these facts we must all agree, but not necessarily with their interpretation. The view which is held here is that cancers, though the product of cells at an embryonic, or too early stage of development, are manifestations of an activity which is characteristic of the other end of life. They are not expressive of the first childhood of the cell, but of its second. Were cancers the direct outgrowth of embryonic cells which have remained embryonic from the beginning, we should expect that they would occur during the earlier stages of life rather than during the later. The period most favoured ought to correspond with the period of higher cell activity, and gradually to lessen as the youth of the body is left behind. But the facts are almost the reverse. Cancers are diseases of the declining periods of life, and are inseparably connected with degeneration—with the breaking-down process, and not with the building up, and their appearance is often heralded by outcrops of senile warts, naevi, and fibrons and other excrescences indicative of renewed but ill-regulated growth activity.

It has been previously pointed out that arrest of development does not imply a longer existence, but that, on the contrary, the ill-developed organ is especially prone to break down and become senile. And this applies not only to the organ, but to the other two great divisions of animal structure; for the imperfectly developed individual and the imperfectly developed cell are alike prone to undergo premature old age and senilism. Moreover, there is very little likelihood of immature cells suddenly waking up from their dormant condition and starting on a process of impulsive growth except as

* See Monti, 'The Fundamental Data of Modern Pathology,' N.S.S. Trans., p. 51.

the expression of a reversal of development. Such a conception of malignancy is quite contrary to all that is known of development and its diseases. It is far more likely that cancer-formation is a developmental change, pure and simple, and that it is started by the supervention of senility in the morbidly immature cells which constitute "rests" and other pre-cancerous conditions. The first childhood of the cell is one of construction and restraint, but the second childhood is distinguished by its lack of restraint, and by its liability to become aggressive or parasitic. Hence, to make a cancer it is not sufficient that cells should be ill-developed. They must also become prematurely old, and must go through second childhood to second infancy until they again become embryonic and multiply with all the rapidity that is usual with cells of a low scale of development. But enough has been said for the present. This subject is one which is intimately bound up with that of the degeneration of organs, and will be alluded to again later on.

The Reversion is not Complete.

Cells which revert to the embryonic standpoint still retain some of those properties which have been ingrained by long inheritance. This is proved by the way in which the secondary manifestations of cancer show the marks of their seat of origin. This is the case, for example, with cancer of the thyroid gland, which is prone to occur metastatically in bone, and especially the bones of the skull. Under these circumstances the cells of the distant tumours may continue to excrete colloid material, like that which is found in the thyroid gland itself. Cancer-cells from the breast have also been known to secrete milk. But at times the secondary deposits apparently show that they are capable of doing the work of the particular organ in which they happen to be engrafted. Thus it has been noticed that in a patient afflicted with cancer of the prostate, with secondary foci in the bones, these distant tumours have the power of forming new bone.* It has furthermore been pointed out that such osteoplastic growths occur in the case of any secondary carcinoma involving bone. In such instances as these it is improbable that the disseminated cancer-cells have forgotten their own special work in favour of that peculiar to the type of tissue in which they happen to be placed. It seems much more likely that the actual cancer-cells remain always the same, and that the formation of bone is really brought about by that secondary influence which cancer

* 'Brit. Med. Journ.,' 1905, vol. i, p. 775.

exerts on the tissue it invades. Recent research tends to emphasise the conclusion that one of the most striking features of cancer is the consistency with which its engrafted cells continue, say through mouse after mouse, to adhere to the type of the original, or parent tissue.

Relation to Normal Old Age.

All this leads up to the point with which we are most concerned. What is the physiological precedent upon which the pathological process of malignancy is based? The formation of a cancer is evidently one of retrogression of cells to an extremely primitive form. And retrogression and degeneration are identical. Now, we know of only one form of natural physical degeneration, and that is the retrogression of old age. Dr. Bashford,* in referring to this subject, says that all the well-known hypotheses of the origin and nature of cancer break down before the problem of its "age-incidence." He shows that this age-incidence is a remarkably consistent feature of the comparative pathology of the disease; for just as cancer appears as a rule after forty-five years in man, so also it favours a corresponding period in the lives of lower animals. "The interval of relative freedom is, in consequence, proportionately much the same for different animals." Sir Jonathan Hutchinson's words in this connection are so pertinent that we quote them in full:† "Sometimes it is not so much senility of the entire organism as what we may term local senility, an old age of the tissues concerned, which is primitive, and does not correspond with that of the body as a whole. Nor, indeed, is it correct to say that the degree of senility is the measure of proneness to cancer, for it is not in conditions of advanced senile atrophy that cancer is most apt to occur, but rather in its commencement. Tissues and organs which are just passing out of use, which are just commencing to decline, are those which are most prone to develop it. Of this law, the female breast offers us the best and most instructive example. It is quite possible that it is under this head that we ought to place part at least of the influence which previously existing local disease appears to exert in evoking cancer. Nævi and other forms of congenital excess, as well as certain innocent forms of new growth not congenital, are, as is well known, liable to be attacked by cancer.

* 'Lancet,' 1905, vol. ii, pp. 838, 1672.

† "Local Origin of Malignant Growths," 'Brit. Med. Journ.,' 1883, vol. i, p. 55.

It may be that these growths run through their life more rapidly than normal structures, and thus, on the score of senility, become liable to cancer earlier than the rest, and it is not improbable that this, too, is the way in which long-continued local inflammation acts, exhausting, as it were, the vital vigour of the part affected, and reducing it to the level of much older individuals. In this way local inflammation may play the part of both predisposing and of local cause."

Dr. Woods Hutchinson* has pointed out that this age-incidence is observed by the sarcomata, for by far the commonest age for the occurrence of sarcomata is between twenty and forty, when "the mesoblast of the body-framework, having reached its highest development, begins its slow decline to old age." In other words, sarcoma would appear chiefly to attack tissues which are losing their vital activity.

Sir Jonathan Hutchinson's views in regard to the age-incidence of cancer are remarkably borne out by the statistical investigations of Professor Karl Pearson,† who comes to the conclusion, as the result of an examination of the figures obtained from 3000 cases, that the liability of women to cancer begins above sixteen, reaches its climax at forty-six, and diminishes until ninety-nine. In men it begins at two, reaches its climax at fifty-six and diminishes until ninety-one.

It is of great importance that we should fully realise what is involved by a return to an embryonic or quasi-embryonic condition of cell life. The quasi-embryonic cells have not started on a fresh cycle, and cannot therefore go on to rejuvenation, and so proceed to a repetition of the events of the old life. What has happened is that the cells in the course of their retrogression have arrived once more at an elementary or unicellular stage, but have at the same time retained a certain measure of the faculty of co-operation, a legacy derived from their old habits. They have reached the lowest rung of the ladder, and there they remain, ceaselessly dividing.

* 'Human and Comparative Pathology,' p. 240.

† 'Archives of the Middlesex Hosp.,' 1902, vol. ii, p. 127.

VIII

INTERMEDIATE GROUPS

Normal granulation-tissue is an intermediate tissue, and, like all other tissues, is liable to become excessive, and to form tumours. These tumours are prone to take up a midway position between *overgrowth* and *degeneration*. So, also, when cancer is originally diffused throughout an organ, it is often more fibrous, and less malignant, so that it does not disseminate. In such cases the cancer may be regarded as intermediate between *cell degeneration* or cancer, and *organ degeneration*.

THOUGH they are radically different, there is no sharp line of distinction between growth and development, and neither is there between the degeneration of cells and the degeneration of organs. Some cancers are less malignant than others, and among these milder forms are a few which approach the innocent tumours or the more widespread degenerations in their course and results. If a cancer be essentially a reversion to a single cell existence, it must necessarily follow that the most cancerous cancers are those in which the cell elements resume the greatest measure of independence. This is well stated by Dr. Powell White,* who says: "Those cancers in which the cells remain independent of each other are the most malignant. For instance, among carcinomata the cells of the columnar-celled type most readily form tissue (epithelial tubes), and this is the least malignant species. On the other hand, cells of the spheroidal-celled carcinoma show very little tendency to form associations *inter se*, and we find that spheroidal-celled carcinoma is the most malignant form." Although semi-malignant or semi-innocent tumours are to be found occasionally among nearly all kinds of cancers, yet they occur much more often in some forms than in others. It is, in fact, possible to separate these mid-way cases into two groups, one of which connects malignant with innocent neoplasms, and the other malignant degeneration with the degeneration of organs.

* 'Lessons on the Pathology of Cancer,' p. 41.

Group Intermediate between Cell-growths and Cell-degenerations.

Though "recurrent fibroids," some endotheliomata, the myelomata, parosteal tumours are mixed growths and degenerations, yet it cannot be said that any of them forms the constituent of a homogeneous group. They are, on the contrary, merely irregular members of other groups. But there is a form of tumour which is essentially intermediate and constitutes a group of its own, separate from all other groups. This may be said of the growths which spring from granulation-tissue.

Ordinary healthy granulations are constituted of a type of tissue which is itself in a formative stage, and is partly growing by the accumulation of cell upon cell and partly developing into a more perfect order of tissue. Granulation-tissue is, in brief, of an intermediate kind, and the tumours which spring from it are also prone to be intermediate.

They are, indeed, so distinct from all other new growths that, like the chorion-epitheliomata, they form a class of their own. It is important that the tumours referred to should be distinguished from the infective granulomata. The latter are produced by, and are solely dependent upon, a definite cause, but the granulomata now under consideration are either spontaneous in origin, or, if started into activity by some local irritation, do not subside when that cause is removed. They also differ from the infective granulomata in their exuberance, for whereas in the infective granulomata the tumours bear some relation to the degree or quantity of the irritant, in the idiopathic granulomata they do not, but are always excessive.

These spontaneous or nearly spontaneous granulomata may be either innocent, forming no more than a lump of heaped-up granulations, or malignant, and either sarcomatous or carcinomatous, but seeming often to lie midway between these two extremes. Such granulation tumours are, perhaps, most common on the fingers and toes by the side of the nails. They also occur in the nasal septum, where they form polypoid growths and bleed freely on the slightest touch. Sometimes they are scattered over the surface of the body, as in the disease called granuloma fungoides. We have also seen one which had arisen from granulation-tissue formed round a concretion in the vermiform appendix. Some of these granulation tumours are so nearly on the verge of malignance as to present all the naked-eye and microscopic characters of cancer without being

actually malignant. They are apparently so close to the border that they sometimes cross over and become cancers.

The following is an account of some varieties of these semi-malignant granulomata.

1. Granuloma of the Nasal Septum.

One of the best instances of a disorder of cells which takes a position between sarcomata on the one hand and benign tumours on the other is the bleeding polypus which springs from the nasal septum. In a comprehensive paper on this subject written by Dr. Pegler,* it is shown that though these growths must be regarded as benign, they, in some respects, simulate malignancy. They are often of rapid growth, have an equivocal appearance, and show a strong tendency to recur after excision. There is reason to believe that they spring from granulations, and Krieg has seen them as conical papillæ of granulations just budding out from the front aspect of the septum. He traces their origin in some cases to the ulcerations which form on parts affected with rhinitis sicca. This is of especial interest in connection with our subject, because rhinitis sicca is, speaking generally, a spontaneous or semi-spontaneous atrophy of the mucous membrane of the nasal cavities, prone to occur in families, and often associated with syphilis or chronic alcoholism. Rhinitis sicca is to all appearance an exaggerated, or premature, degeneration (senilism). Many instances of bleeding polypus have in the past been regarded as myxo-sarcomata, and others, more recently, and by excellent authorities, as angeio-sarcomata, sarcoma telangiectoides, endothelial angeio-sarcomata, or angioma cavernosus sarcomatodes. Further, they are closely related, as Dr. Pegler points out, to the aural polypi, for these also start as growths of granulation-tissue, and are sometimes sarcomatoid. We have seen one such tumour. It occurred in a married woman, aged 28 years, who was sent to us by Dr. Evans, of Goring, some twelve years ago. When we saw her a dark purple softish mass was projecting from the right nasal orifice. It had on several occasions bled so freely that the woman looked decidedly anæmic, and we handled the growth with the utmost care lest more blood should be lost. We subsequently cleared out the nostril rapidly with a curette, after

* "The Pathology, Affinities, and Treatment of so-called Bleeding Polypus (Discrete Angioma) of the Septum," Dr. L. H. Pegler, M.D.Edin., 'Lancet,' 1905, vol. ii, pp. 1455 and 1537.

plugging the posterior nares, and then blocked the anterior opening. Three days afterwards the nostril was washed out, and fresh growth was seen to be already springing up from the bony septum. The upper lip was therefore lifted up after Rougé's method, a red-hot fenestrated tongue forceps was then pushed into the nose, and the bony septum was wrenched out. When we last saw this woman about three years afterwards she was strong and well, and was in no way the worse for the operation.

2. *Digital Granulomata.*

We also meet with similar growths in other parts of the body. One of the most common is that found by the side of a finger- or toe-nail, due either to some irritation of or about the nail or to injury. As a rule they are mere heaps of granulations, and go away as soon as the irritant is removed. But now and then they are more troublesome, and occasionally are semi-malignant or even downright cancers. The following examples are arranged in an ascending scale of malignancy :

(1) *Innocent*.—A lady, aged 38 years, had a whitlow of the thumb. As this went away granulations sprang up at the base of the nail, and within three days had become decidedly exuberant. They were touched with nitrate of silver. At the same time the base of the nail was cut away, and some concealed granulations were liberated. But in two days' time the granulations were more vigorous than ever, so that the whole of the space made by the removal of the nail was filled with a projecting soft red lump. A section of this growth was inspected under the microscope, and found to consist of a basis of granulation-tissue containing but few blood-vessels, and covered by a very irregular layer of epithelium. This last dipped deeply into the subjacent tissue, and *seemed* both to cut off islands of this tissue and to be itself in places surrounded by it. The whole of the nail was now taken away, the granulations were sheared off to the level of the nail-bed, and no further trouble was experienced.

(2) *Semi-malignant*.—A youth, aged 19 years, a drover, was bitten on the thumb by a sheep. As the wound healed a crop of granulations sprang up by the side of the nail. In spite of the use of antiseptics, nitrate of silver, and other remedies, the tumour continued to grow, and to spread out at its base until it was more than three times its original size, so that when we saw it six weeks after its formation it was 1·4 cm. in length and nearly 1 cm. in

width at its base. It was florid and prominent, and had lifted the half of the nail from its bed. There was no sign of inflammation, and a radiogram showed that the last phalanx was undergoing absorption. The tumour was shaved off and examined microscopically, and was pronounced by the Clinical Research Association a spindle-celled sarcoma (?). The thumb was amputated at the Royal Berkshire Hospital through the middle of the first phalanx. On examination of the growth it was found to penetrate into the last phalanx, half of which it had destroyed. No recurrence had taken place when we last heard of this patient about two years later.

(3) **Semi-malignant.**—A single lady, aged 21 years, came to us with a small granuloma of the inner fornix of the left index finger. It had sprung up without any definite cause, and when we saw it, had existed for about a fortnight. Of the size and projection of a split-pea, it was oval in shape, granular, and florid, like the wattle of a cock. An aunt had died from sarcoma of one kidney, a brother from sarcoma of the testicle, and an uncle subsequently succumbed to pernicious anæmia. We destroyed the granuloma with repeated applications of nitrate of silver, and had the finger dressed with phenol solution, but the growth soon reappeared, and within a fortnight was as big as ever. It was then cut off and examined under the microscope, but nothing could be seen except granulation-tissue covered by a thin line of epithelium. Nevertheless, it soon came back and was therefore destroyed with ethylate of sodium, and nearly half the nail was removed at the same time. But as this was no more successful than the former treatment we removed the rest of the nail, and carefully cut away the whole of the diseased area. The growth was then found to dip into the underlying tissue and to radiate in fan-like manner with a vertical fibrous striation. This more radical treatment was even less satisfactory than the other. The growth re-formed and soon stretched half way across the nail bed. We therefore obtained the benefit of Dr. Marriott's opinion, and this coinciding with ours, we advised removal of the whole finger. This was accordingly done, and no recurrence has taken place, though the operation was done five years ago. A section through the finger at the part affected shows an aggressive growth of spindle-celled tissue invading and destroying the bone, but its character does not seem to be distinctive of either granulation- or of sarcoma-tissue.

(4) **Malignant.**—A man, aged 48 years, was brought to us by Dr. Truman for a granulation tumour growing from the outer fornix of

the second toe of the right foot. There had been no definite injury, and the growth looked in every respect like that which was present in the last case. Dr. Truman had been treating it for five weeks with various ointments and dressings, and had also applied nitrate of silver without doing more than temporary good. We now destroyed it with ethylate of sodium, but it speedily returned, and as it was thought unsafe to continue the same line of treatment the toe was removed forthwith. The wound had hardly healed when a few slightly enlarged glands were found in the upper part of the thigh and groin of the same side. As there had been no sign of inflammation of the tumour, and no lymphangitis, it was decided that the increase in the size of the glands was due to secondary cancerous infection, and they were immediately taken away. Other glands in the groin were soon involved, rapid cachexia set in, and, though these glands were also removed, it was of no avail. The abdominal glands became implicated, and death resulted from emaciation and debility within four months from the first appearance of the tumour.

3. A Granuloma round a Concretion in the Vermiform Appendix.

This example of a borderland growth springing from granulation-tissue came under our own notice in 1898, and was described in the 'Lancet' of that year. The patient was a woman. The growth was of the size of a fist and contained a few small abscesses. To the naked eye it had the appearance of a sarcoma. It was a sharply defined hard tumour, so incorporated with the bowel adjacent to the vermiform appendix that some 8 cm. of colon and small intestine had to be taken away with it. Moreover, nodules of growth projected into the iliacus muscle so that some of this muscle was perforce removed at the same time, while the ilio-inguinal and external cutaneous nerves were embedded in the tumour to such an extent that a few inches of each had to be cut away.

The part removed, together with a microscope section of the growth, were shown at a meeting of the Reading Pathological Society, and those who were present agreed that the growth was a sarcoma. All the cells were big and spindle-shaped, and no round cells could be detected in the specimens examined. At the same time it is true that no intervening fibrillæ could be found between the cells.

Yet, that the growth was innocent can, we think, hardly be doubted, for the patient is still alive and well, and has never had any further trouble in that part of her body.

In each of these cases there was a definite tumour, which, in its beginning, there is reason to believe, was perfectly innocent. One of them—that round the vermiform appendix—was to all appearances (microscopic and macroscopic) a spindle-celled sarcoma, but clinically it was benign. The nasal tumour was clinically and microscopically innocent, but its naked-eye appearance was that of a sarcoma. Of the digital growths one eventually became a true virulent carcinoma. The other three, to the naked-eye, looked exactly like it. One was destroyed after only a few days' growth, but the other two had enlarged their boundaries, though there was no inflammation, speedily recurred after removal, and were so aggressive that their cells had penetrated the structures beneath them and partially destroyed the bone. They may, therefore, with reason be regarded as either on the borderland of malignancy or as actually malignant. To our mind suspicious elements about case No. 3 were the apparent presence of heredity and the absence of ascertainable cause. In case No. 4 the growth also appeared to be spontaneous.

Jensen's mouse tumour.—Mr. Roger Williams* has made some observations which are *à propos* this subject of intermediate growths. He is emphatically of the opinion that the tumour which is produced by the grafting of mice with cancer is not cancer, but is quasi-malignant only. He says that “wherever epithelial cells capable of proliferation come into contact with proliferous granulation-tissue they grow into and inter-penetrate the latter, producing histological appearances which are *per se* often indistinguishable from cancer.” He refers to erosions of the cervix uteri as “commonly comprising epithelial structures exactly like cancer structures,” and also to the contagious venereal tumours of dogs, which were at one time regarded by highly competent observers as cancers.

4. Multiple Granulomata; Granuloma Fungoides.†

This disease, which is usually known by the tautological name of “mycosis fungoides,” is generally preceded by some form of dermatitis or by recurrent attacks of lymphangitis. The antecedent “inflammation” is usually erythematous or eczematous, though it may be a psoriasis or a pityriasis rubra.

Granuloma fungoides occurs as a rule between forty and fifty.

* ‘Trans. Path. Soc.’ vol. lviii, 1907, p. 38.

† Extracted from the article in Dr. Radcliffe-Crocker's ‘Diseases of the Skin,’ ed. 3, vol. ii, p. 976.

It is regarded by some observers as of lymphatic origin, the nodules being classed with those seen in Hodgkin's disease, which they closely resemble in structure. They consist of masses of round cells supported by a delicate and scanty reticulum. Their course is often of a fluctuating nature, and Dr. Radcliffe-Crocker has seen the disease while as yet in an early stage spontaneously disappear. But as a rule ulceration sets in with resulting cachexia, and ultimately, after an interval of months or years, death occurs as the result of streptococcal intoxication from the fungating sores.

The disease is of local malignancy; in other words, it is, as a rule, confined to the skin or mucous membranes, and no particles are thrown off to infect other organs. But in a few cases it has proved itself to be a true cancer by disseminating itself into one or more of the viscera.

In one case recorded by Bazin recovery took place after an attack of erysipelas. In another the disease disappeared as the result of X-ray treatment (Allan Jamieson). Improvement may be produced by arsenic, but generally speaking the disease is fatal.

Group Intermediate between Degenerations of Cells and Degenerations of Organs.

It has already been pointed out that when any organ undergoes fibrous or an allied form of degeneration, and such degeneration, instead of being diffused through the whole of its structure, is localised into one part, this localised degeneration is usually apt to be the starting-point of cancer formation. And *per contra*, when cancer is distributed through an organ a compromise is effected between the cancer and the ensuing fibrous degeneration, with the result that the new tissue resembles ordinary fibrosis on the one hand and local malignance on the other. Examples of both of these half-way forms of degeneration have already been given. These are sporadic instances, but states intermediate between the degeneration of entire organs and of single cells also occur in group form.

The group referred to is that of the degeneration of the lymphatic system. We have just mentioned a group which comes between the growths and degenerations of cells, and have shown that it owes its intermediate position to the fact that it arises in an intermediate form of tissue, to wit, granulation-tissue. So also the degenerations of the lymphatic system take a half-way place, because they, too, have their physiological basis in an intermediate tissue, for the elements of which they are composed are almost as truly indepen-

dent cells as the restrained members of a community. Lymphatic tissue, in fact, takes a half-way position between the cell and the organ. Each gland acts as a whole under certain circumstances, while under other circumstances its constituent cells—lymphocytes—migrate and live an independent life. Hence the forms of degeneration or senilism which affect organs or cells are also duplicate or intermediate. These degenerations are known under the names of “leukæmia,” “Hodgkin’s disease,” “splenic anæmia,” etc.

Of these and others of their group we may say that, though cases occur which seem to take a slow course and to behave like the usual run of degenerations of entire organs, quite as often their behaviour is much more like that of the sarcomata or endotheliomata. Speaking generally, it seems impossible to say whether they are of the nature of malignant degenerations or should be regarded in the same light as cirrhosis of the liver, *i. e.* as degenerations of organs. But the discussion of this subject must be reserved for the chapter on the degenerations of the blood-forming organs and of the liver.

One more link of connection between cell degeneration and organ degeneration must, however, be referred to here. Mr. Lenthal Cheate* has called attention to the liability of some skin cancers to be roughly limited to the area of distribution of certain cutaneous nerves. It seems probable that in these cases the cancer is manifesting similar tendencies as when it diffuses itself over a liver, a gall-bladder, or a stomach. When any tract of tissue comes under the sway of some particular nerve it has gone part of the way to differentiate into an organ. Such a tract would consequently tend to uniformity in its diseases to the same degree that it is uniform in its physiological aspects.

* “The Behaviour of Cancer within Nerve and Trophic Areas,” ‘Brit. Med. Journ.,’ 1903, vol. ii, p. 1515.

IX

CONCLUSIONS TO SECTION II

Cancer is a senile degeneration affecting single cells. Having prematurely arrived at their normal second embryonic life, the cells follow the course of all cells of low unicellular type by multiplying incoherently. They have not in reality lost every vestige of control, for they continue to show the influence of the co-ordinated tissue from which they spring. Cancers are reversions or regressive variations of cells in their individual capacity. They are either cryptogenous, and heritable, constituting major variations, or are the result of causes and are minor variations.

THE human body is composed of two kinds of cells : one for its owner's particular use, and the other for the perpetuation of the species. The latter or reproductive cells are either set apart from the beginning or are specialised out of somatic cells. They are encapsuled and packed away within the somatic cavity, where they remain dormant until circumstances arise which liberate their activities. It is obvious that the potentialities of this form of cell are immense, and are at first manifested mainly in the form of proliferation. They multiply prodigiously. But this faculty of multiplication is kept under the most perfect control, so that it is carried exactly to the desired pitch, and no further. Nothing, indeed, can be more marvellous than the way in which the original reproductive cell proceeds to duplicate and to form ranks, tubes, coils, sheets, and solid masses of co-ordinated cells, and, having arrived at a certain point, gradually to cease. Indeed, in this process of vigorous proliferation the cessation is quite as amazing as the multiplication.

Cells are set apart from the general somatic cells and appropriated for this process of organised proliferation at a very early stage of embryonic life. And if, from any cause, some of the cells of the fully developed animal should reverse the stages of their development, and should go back to their primitive simplicity, it is conceivable that they will at last arrive at a stage from which they can start anew on a process of similar multiplication. But the multi-

plication cannot now be of that regular description which characterises normal reproductive activity. It is a backward or retrogressive, and not a progressive process, and can therefore have no outcome in the formation of a definite organism, nor can it ever come to an end. Moreover, it is not a sexual process, for the cells represent a unicellular stage of existence at a period of development prior to the formation of sex.

Of such a description are the cancers. They have their starting-point in some cell or cells which have gone back through their period of second childhood to a still earlier, or quasi-embryonic, stage.

Cancers, therefore, crop up towards the end of the functional life of any particular organ or tissue, and are peculiarly liable to occur in organs which have undergone degeneration.

It is doubtful whether they ever spring from cells of normal development, but anything which facilitates proliferation, reducing cells to their primitive simplicity, paves the way for cancer formation. Hence we can enumerate at least four conditions which may be termed "pre-cancerous" stages of cancer.

These pre-disposing conditions are provided by—

(1) Cells of imperfect development, or in a state of infantilism, as in the so-called "rests."

(2) Cells which have already partially reversed their development prematurely, or are in a state of senilism, as in—

(a) pre-senile degeneration of organs,

(b) innocent growths with incidental degeneration.

(3) Normal senile tissues.

Like normal reproductive tissue, cancer consists of masses of proliferating cells divided into groups by fibrous septa and separated off from the surrounding somatic cells by a rough and irregular border or spurious capsule of fibrous tissue. They also disseminate themselves into distant parts by means of seed cells. Like normal reproductive cells, too, their elements may, under favourable circumstances, be engrafted into the bodies of other animals of the same species and may there multiply, always reproducing the features of the original stock.

On examining such cells under the microscope it is found that some of them show the peculiar nuclear changes which were believed by some observers to be characteristic of reproductive tissue. At any rate among the cells of cancer are some which show changes indicative of extraordinary reproductive activity, and these changes are in the animal kingdom present in the same degree in normal reproductive cells, and, it is said, in them only.

But of all the cells in the normal body probably none has a closer affinity with the cancer-cell than have the white blood-cells, for these, too, represent low degrees of development, with a high degree of proliferating activity. Moreover, it is an activity which resembles cancer formation and reproductive proliferation in being liable to be called forth by special circumstances (*e. g.* wounds, microbic invasion).

Hence, any method of treatment which will stop cell proliferation is calculated to put a check to (1) cancers, (2) the special function of reproduction, and (3) the function of leucocytes. This is, in fact, accomplished by radium and X-rays, and nothing seems to point more strongly to the conclusion that the virulence of cancers rests in their proliferative activity than the fact that the primitive reproductive cell and the primitive white blood-corpuscle both resemble the cancer-cell in being especially vulnerable to the influence of X rays.

A cancer is a compromise between degenerated cells and the normal cells of the body. It is the immaculate but illegitimate conception of the tissue in which it has its being. Each cancer breeds true, and has its species determined by the nature of its parent tissue, so that if it originate in epithelium the offspring bears the marks of its parentage and remains an epithelioma, no matter how often it may be engrafted or disseminated, and so also, in like manner, with connective-tissue cancers and with other cancers. A cancer is, indeed, the result of the partial reversion of immature or adult cells to a quasi-embryonic state, and the virtual creation of a new species of low organisation out of the adjacent parent tissues.

These are the special aspects of the pathology of cancers and cancer formation. They are corroborated by a general review of the nature of cancer, for if we subject it to the tests which have been referred to we shall find that it is an intrinsic rather than an extrinsic disease, and is distinctly a disorder of development. This is proved by the facts that it arises as a rule without obvious cause, is progressive in its course, but often very irregular, so that the disease is in abeyance or smoulders at one time and flames out at another, and does so without any obvious cause. It occasionally happens that the inhibitory phase is so marked that the progress of the cancer is permanently arrested or actual absorption takes place. The disease, moreover, is not obviously influenced by normal vicissitudes of progressive development, though its onset may be determined by the changes which take place during the periods of retrogression.

But at this point cancer degeneration diverges from organ

degeneration, for there is no satisfactory evidence that cancer is ever started into being by those more general causes which are more or less responsible for the onset of the developmental disorders of organs and of the whole complex individual. In short, cancer is essentially a *local* disease of single cells. It therefore follows that when causes can be found these causes are always local, and are of the nature of injuries or irritations. Nothing better illustrates this fact than alcohol. It has never clearly been shown that alcohol gives rise to cancer of the body in general, though there is reason to believe that it may act as a secondary or contributory cause. But there seems to be but very little doubt that the drinking of spirits accounts for some cancers of the lips or tongue. In other words alcohol, when its action is concentrated upon certain cells, may bring about their degeneration, but diffused over the body it is almost innocuous so far as cancer is concerned. It then comes into contact with organs, acting upon them in a diluted form, but for much longer periods, upsetting their equilibrium and becoming responsible for their degeneration.

And just as the causes of cancer are such as are calculated to affect single cells or cell groups, so also the anatomy and treatment of cancers is indicative of a local cause and a centrifugal extension. In brief, everything points to the conclusion that cancer is a reversion or degeneration, that it is a degeneration of single cells, and that those influences which affect the organ or the individual at large are of very little consequence in directly giving rise to cancer, though cancer is liable eventually to spring out of them. They do no more than prepare the way for cancers.

Up to this point we have been forestalled by Sir William Collins,* and we cannot do better than repeat his words, for though he has since elaborated this doctrine, his short statement of 1888 can hardly be improved upon. This solution of the cancer problem has been favourably received by those most competent to judge. He says cancers "lack the influence which makes for organisation; their instincts are of the lowest—are amœboid, in fact. They possess the fecundity of cells unfitted for colonial life, and share their vagabond propensities. Herein lie the factors of malignancy, the causes alike of the rapid growth and of the infectivity of cancer." He regards cancer as a "persistence of (Cohnheim), or reversion to, that still earlier type of a structureless cell, inept at specialisation, indisposed to colonial collaboration, and multiplying by fission with that terrific rapidity characteristic of the lowliest of living things."

* 'Lancet,' 1888, vol. ii, p. 395.

The factors which constitute cancer malignance consist of the abnormally premature senility of cells on the one hand and the youth of the surrounding tissue on the other. The relapsed embryonic cells are alien to their environment. One result of this want of sympathy is that the younger in life a cancer appears the greater is its virulence. In old age the tissues in general are ripe for degeneration, hence bands of contracting fibrous tissue are soon formed round the cancer-cells, tending to shut them off from encroachment on healthy tissue. But in young life the cancer-cells are less readily encapsuled, so that they penetrate easily, and the cancers of which they form the constituents are soft, of rapid growth, and of a high degree of malignancy. Cancer, being a senile change, adaptation is easy in old age, difficult in youth.

Biological Aspects of Cancer. Cancer as a Variation.

All that has now been said tends to the conclusion that cancers are variations of the development of individual cells.*

They are regressive variations because they swing back in their development to a period which corresponds with the embryonic stage of ontogenetic development, and with the unicellular or protozoan stage of phylogenetic development.

The variations are of two kinds: (a) Minor or continuous; (b) major or discontinuous.

(a) That some cancers are instances of **minor or continuous variation** is shown by the way in which they appear in response to environment (for example, that implied in irritation by soot, arsenic, alcohol, and tobacco). But environment alone will not account for their appearance. Something more is needed, and this something is called "idiosyncrasy," "proclivity," or other equally nebulous term. Yet it is impossible to be more explicit, for even when we describe it as an inborn tendency to vary we are no nearer to a definition, though the idea connoted may be more exact.

* In an address delivered before the Australian Medical Congress at Adelaide in September 1905 Professor D. A. Walsh, of Sydney, gives an excellent review of recent studies in the minute histology of malignant disease, and emphasises the importance of biological considerations. He dissects the significance of the heterotypical mitoses which sometimes occur in senescent tissues, and arrives at the conclusion that tumour growth may, perhaps, prove to be a natural phenomenon determined by a definite concatenation of natural circumstances, amongst which the senescence of the particular tissue concerned is regarded as being especially important. If this view be corroborated by further investigations, "the nature and origin of cancer," Professor Welsh declares, "will essentially be a problem of biology, and only accidentally a problem of pathology," 'Lancet,' 1906, vol. i, p. 881.

At any rate, there are two factors to be reckoned with in the origin of most cancers, the one being an external cause or environment, the other a cryptic tendency to vary, probably a reminiscence of some bygone character, or of some great epoch in the evolution of the animal kingdom. Max Borst, in his great work on tumours,* dwells upon the importance of this concealed factor. He says that though tumours may be brought out by certain secondary causes of the nature of irritation or inflammation, in reality they owe their being to some more deeply seated cause. It is only in this way, too, that he can account for the sudden appearance of cancer in a seemingly healthy organ.

(b) We cannot account for the origin of some cancers. This does not always mean that we are merely ignorant of the cause, and that this cause will some day be revealed. On the contrary, there is every reason to suppose that in some cases the cancer appears spontaneously as a **major or discontinuous variation** of individual cells. This may be suspected more particularly when the cancer occurs in a young subject—that is, during early progressive development. When, in addition, there is plain evidence of heredity, variation and variation alone will account for the appearance of the cancer.

Though we can say that certain cancers are definitely due to the action of some local “environment,” and are continuous variations, and though it seems equally clear that other cancers (*e. g.* retinal gliomata) are discontinuous variations, yet of the majority of cancers we cannot as yet say dogmatically to which category they belong.

* ‘Die Lehre von den Geschwülsten,’ Bd. i, S. 79.

PART III

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF ORGANS

INTRODUCTION

Organs defined. Disorders of post-natal growth and development of the extremities.
General classification of the disorders of post-natal growth and development of organs.

It has been stated, as an almost self-evident truth, in the earlier part of this book, that every physiological act or condition is liable to fall short of or to exceed its proper degree; and that every cell, organ, or individual is liable to be too big or too little, too tardy in developing, or too soon in coming to perfection. Moreover, this failure or excess may be so pronounced as to constitute disease, and from this disease no part of the body is exempt. As a matter of fact, we shall find that certain parts are far more prone to one or other of these extremes than are the tissues in general. These are the terminal parts or organs, by which is meant those parts which, like the hands and feet, the breasts, the liver, the kidneys, brain, and testes, are the termini for networks of blood-vessels, lymphatics, and nerves. They are the specialised ends of the body, set aside for particular purposes, standing out conspicuously from other parts by virtue of their higher development, and, in consequence of their higher development, peculiarly prone to lose their normal balance and become the seat of disease.

It is fitting that we should begin with an account of the faults of growth and development of the extremities, seeing that these are parts which can readily be inspected. Moreover, as the hands and feet are not essential to life, their diseases may go on to a far more advanced degree than is possible with corresponding diseases of internal and more vital organs. Above all, the giant hand, as we shall presently see, constitutes a connecting link between pre-natal and post-natal disorder, and illustrates remarkably well the relations of excessive growth to premature old age.

And this, perhaps, is the most appropriate place in which to insist that though we have hitherto referred to the four primary disorders—to wit undergrowth, overgrowth, infantilism, senilism—as clearly defined entities, it will soon become evident that this is by no means invariably the case. As a rule, they stand out prominently

one beside the other, but they have their meeting grounds, and it may be very difficult to say to which denomination a particular case belongs.

Difficulties of this sort may arise from the degeneration originating in an organ of defective development. It may also be almost impossible to say whether a given organ is of defective development or is merely of defective growth. The incidental degeneration of overgrowth, again, is, in the case of some organs, so prone to lead on to the complete breakdown of unmitigated degeneration that we may be unable to distinguish between them.

Hence, as we go on it will become more and more evident that the primary disorders of development do not consist solely of two kinds—infantilism and senilism—and that degenerative hyperplasia, intermediate between overgrowth and over-development is of great importance.

A convenient way of classifying these disorders is as follows:

1. Undergrowth. 2. Under-development.

Dwarfism and infantilism are, as we have just said, peculiarly difficult to separate. There can be no doubt that deficiency of size does occur, apart from deficiency of quality. We recognise this with fair readiness in the case of the man, and of some organs, such as the hand, or the brain; but in other cases, and especially in that of the deeper organs, so little is known of the distinction between the two that we shall often have to take them together.

3. Hyperplasia or Overgrowth.

This is commonly called “hypertrophy,” and consists in reality in simple overgrowth of all the constituents of a part, function being also carried on to a corresponding excess.

As a matter of fact we can distinguish two kinds of overgrowth.

One is the result of progressive development being carried a little too far, so that both structure and function are over-abundant, as in the thyroid gland of Graves’s disease, and the muscles of the strong man. This is consequently a progressive variation.

The other form of overgrowth seems to be due to a slight loosening of growth restraint due to a mild degree of degeneration. If this view of its origin be correct it is a regressive variation. It is exemplified in the parenchymatous goitre which appears in the declining periods of development in women.

4. Degenerative Hyperplasia.

This consists in overgrowth with loss of function. A good example is the big goitre arising from degeneration of the parenchymatous goitre of Graves' disease. Sometimes the overgrowth and the degeneration appear to go on simultaneously from the beginning. This is apparently what happens in the giant hand, and in many cases of so-called "hypertrophy" of the pylorus in infants, in "hypertrophy" of the female breast and of the tongue, and in "hypertrophic" cirrhosis of the liver. It may be conjectured that even in these cases there is, in reality, a primary overgrowth. Degeneration of this hyperplastic type sets in, seldom during the declining periods of life, but usually during the time of greatest functional activity.

5. Degenerative Hypoplasia or Senilism.

In the degeneration which is characteristic of senilism the organ is shrivelled and manifestly senile. The process is a caricature of normal old age, and is well exemplified in facial hemiatrophy, where one side of the face may look ten or more years older than the other side. It is also seen in granular kidney, and in atrophic cirrhosis of the liver. But though the organ is small and shrivelled and degeneration is the main feature, it is important to realise that there is always hyperplasia as well. The number of cells in the organ is increased, but this excess is brought about by the formation and proliferation of an embryonic, small, round type of cells. At the same time, as the organ as a whole is wasted, the process may, for the sake of convenience, be termed "degenerative hypoplasia." Degeneration of this sort may also be but the last stage of degenerative hyperplasia, as when facial atrophy follows scleroderma, or atrophic cirrhosis of the liver follows the hypertrophic form, or the wasted pale granular kidney supervenes on the large white kidney.

Classification of the Diseases of Growth and Development of Organs.

Growth.

1. Undergrowth, or hypoplasia.
2. Overgrowth, or hyperplasia.

Development.

1. Defective progression, or infantilism.
2. Premature regression, or senilism.

SECTION I

The Disorders of Post-Natal Growth and Development of External Organs.

I

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF THE EXTREMITIES

Overgrowth shades off into mere asymmetry on the one hand and degenerative hyperplasia on the other. **Degenerative hyperplasia** is of many *varieties* but there is always a tendency for the most specialised tissues to be affected most often and most severely. Generally of pre-natal origin, its cause is, as a rule, unknown, but it may be due to injury, or to syphilis. *Diagnosis: Elephantiasis arabum*, and spontaneous local macrosomia, and in all probability *hereditary œdema*, though widely different, are connected by intermediate links. *Aeromegaly* is a general, not exclusively local, disease. The *hereditary* transmission of giant growths of the extremities is very exceptional, but a similar affection of the gums occurs as a family disease. The *course* is progressive, and is either uniform or intermittent. The *results* are probably unfavourable as a rule. *Treatment* by elastic compression is unsatisfactory; that by arterial ligature or amputation is more successful. Bleeding or inflammation is apt to prove troublesome or even fatal, and growth sometimes continues after the operation. Local macrosomia occasionally occurs in *association* with innocent tumours, pre-natal defects, general infantilism, and other anomalies of growth and development. **Structural characters: pathology.**—The tissues affected are of defective nutrition, so that ulcers are prone to form. *Microscopically* the disease is distinguished by reduction of gland- and duct-cells to an indifferent, rounded form, and their transformation into, or replacement by, connective tissue. Similar deterioration with multiplication goes on in bone, muscle and other tissues. **Defective development and degenerative hypoplasia** are different manifestations of the same process of major variation, the one being an infantilism and the other a senilism. They are occasionally *limited to certain nerve areas*, not because of any trophic influence of the nerve, but because the tissues of the part concerned are to some extent segregated or specialised so as to form a rudimentary organ. **Persistent hereditary œdema** is in some ways closely related to the giant hand though it shows important differences in other respects. It is a permanent painless swelling of the soft parts of the lower extremities.

I. Overgrowth or Hyperplasia of the Extremities.

IN some examples of local macrosomia the enlargement is so moderate in degree and so uniform that it is not easy to say whether it should be regarded as a deformity (*i. e.* disease), or whether it amounts only to mere asymmetry, such as is often to be seen in normal individuals. This difficulty arises more particularly when the face is the part affected. In rare instances the facial or other hyperplasia is so conspicuous as evidently to be abnormal, and of the nature of a malformation, but this overgrowth does not as a rule go beyond certain moderate proportions, for when these are attained the hyperplasia ceases. Sometimes, however, after a period of quiescence, growth begins anew, alters in character, and runs on into degenerative hyperplasia. Probably this is the explanation of some instances of local macrosomia, of which it is reported that they were at one time but slight in degree and stationary, but afterwards attracted attention because of their progressive and enormous enlargement. It is not possible always to make sure of this point, owing to the want of detail with which cases of giant growth are too often recorded.

It is rare for anything to be said, for instance, about the functional state of the earlier or slighter forms of this malady.

True functional hyperplasia usually goes by the name of "hypertrophy." Richardière* mentions the occurrence of such a condition. Dr. Montague Murray† also describes a case in a man of twenty-one, in which it was associated with a diffuse cutaneous nævus. The whole of the left upper limb was involved, including the bones, although the man was not left-handed. The left upper extremity was $1\frac{1}{2}$ inches (3·8 cm.) longer than the right, and a dynamometer indicated a grasp of 115" on the left, as compared with 80" on the right side. Mr. Barwell‡ has also recorded an instance of overgrowth of the right lower limb, beginning at about the end of the first year. The child was six years of age, and the limb, which was of excellent intrinsic proportions, resembled that of a child of eight or nine. Movement was perfect, and the part was nearly two degrees higher in temperature than the other.

In such cases as these all the structures affected are enlarged proportionately, and so they may remain. But true overgrowth or

* 'La Semaine Médicale,' 1891, p. 125.

† 'Trans. Med. Chirurg. Soc.,' vol. xvi, p. 359.

‡ 'Clin. Soc. Trans.,' vol. xvii, 1883, p. 225.

functional hyperplasia of this description is prone to go further. The limb, which at first was moderately enlarged, and perhaps a little stronger than its fellow, may some day begin to grow afresh, and as it grows to become weak and deformed, both weakness and deformity being in a ratio roughly corresponding with the size. The limb has now ceased to be merely overgrown. It has in addition become degenerate, and comes under the head of "degenerative hyperplasia."

2. Degenerative Hyperplasia of the Extremities: Varieties.

Many instances of degenerative hyperplasia are to be met with in medical writings, and so greatly do they differ that hardly any two cases are even superficially alike. All the tissues of a part may be involved, either in the same or in different cases. Sometimes one tissue is disproportionately affected from the beginning; at others, as we have already seen, the different structures are at first implicated almost to an equal degree. But as growth continues it nearly always happens that one or more tissues increase much more rapidly than others. In short, all forms of overgrowth may be found, from that which affects all tissues almost to a similar degree, to that which affects one tissue alone. In many cases there is great abundance of fat, and these merge into true lipomata. In others it is the lymphatics which are mainly involved, and some of these are difficult to separate from filarial elephantiasis. Often the blood-vessels are the most implicated, so that the enlargement is nævoid in structure.

External local gigantism is, perhaps, generally noticed in one of the upper or lower extremities, and then, as a rule, it chiefly affects the fingers or toes (macroductyly), hand (macromany), or foot (macro-pedy), or involves more or less of the whole extremity. Sometimes, on the other hand, it is found in the face, when it may be confined to one portion (*e. g.* the region of the lower jaw, gums, or tongue (macroGLOSSIA). Moreover, it may affect more than one part, or it may include the one side of the face, or the half of the head (facial or cranial "hemihypertrophy"). Though it rarely extends to more than the half of the body, it is not very unusual for it to occur in the two corresponding limbs of opposite sides. In very rare cases all four extremities are affected together* (acro-hyperplasia of Arnoné). It has been known to implicate the upper limb of one

* 'Riforma Medica,' Anno xx, 1904, p. 337.

side and the lower limb of the other side (crossed giant-growth); the whole of one side and only one digit (Dr. Shands), or one extremity, of the other side; or to be distributed more or less irregularly over different portions of the body. In Dr. D. E. Jacobson's case* the condition began at birth, with telangiectases of the breast and lower part of the body, and macropedy. At the age of three years, when the account was written, it had resulted in enlargement of the right cheek, right upper extremity, right foot and right labium majus, and of the left half of the trunk and lower extremity, showing itself chiefly in the left foot, especially in its great toe.

The deformity produced by extreme instances of this kind of tissue overgrowth may, if widespread, be so great as to cause the body to resemble the gnarled trunk of an old tree, or some grotesque Japanese carving. Thus Sir Frederick Treves† has described a case in which giant-growth, beginning in the right hand and foot, and the right side of the head, ended in pronounced overgrowth of the whole right upper extremity and both feet, with hideous deformity of the greater part of the head and body. It consisted not only in enlargement of the soft tissues with warty excrescences, but also in bossy overgrowth of the bones of the skull. The unfortunate man was indeed so warped and distorted by the eccentric and redundant growth of his tissues that he was exhibited in shows as an "elephant man," from his fancied resemblance to an elephant. His disease finally brought about his end, for he one day dislocated his neck, owing to the sudden falling forward of his ponderous head during sleep.

Cenas‡ has also given details of his examination of a patient with irregular hyperplasia. Beginning with enlargement of half of the face at birth, a few months afterwards both hands were noticed to be too big. Spots of pigmentation then appeared on the hands and feet, and were followed by overgrowth of those members. There was also enlargement of the whole lower jaw, including the teeth.

Local gigantism reaches its greatest excess in the upper and lower extremities. These may, indeed, be so big that the affected limbs attain more than double their proper size, as is represented in some of Wittelhöfer's figures.§

* 'Virchow's Archives,' F. 13, Bd. ix, 1895, S. 104.

† 'Trans. Path. Soc.,' vol. xxxvi, 1885, p. 494.

‡ 'La Loire Médicale,' St. Etienne, December 15th, 1890 (Sajous's Annual).

§ "Über angeborenen Riesenwuchs der oberen und unteren Extremitäten," 'Langenbeck's Archives,' Bd. xxiv, S. 64.

No part of the external surface of the body is apparently exempt, though a preference seems always to be shown for those parts which are extremities or equivalent to extremities. Thus, not only a finger or toe, but the half or the whole of the scalp, the nose, the ear, the breast, the pudendum, the clitoris or the penis may each be regarded as an extremity, and may be affected in different cases. But now and then we also see similar hyperplasia of tissues which are not extremities, such as of the skin (ichthyosis) or subcutaneous tissue (scleroderma). Even in these cases, however, there is evidently a strong tendency for the disease to be confined within some physiological boundary, for it seldom implicates the skin as a whole, but is either limited within the area of the face, the head, foot or other prominence, or shows a tendency to affect the area of distribution of some nerve, as will presently be shown.

The disease shows a decided preference for those parts which are of greatest physiological importance, and are most differentiated. Thus, for example, the right hand is perhaps a little more often affected than the left—in the proportion, according to Sakler,* of fifteen to twelve.

It may be objected that the giant growths of some parts of the body are not of the same nature as giant growths of other parts. But this objection cannot be sustained. In the first place, it may be shown that the different kinds occur together in the same individual. In the second place, all forms of local gigantism are connected by intermediate forms. Thus, enlargement of the gums may be unilateral and associated with partial macrosomia of some other part of the head or face.† Macroglossia and “hemi-hypertrophy” may go together.‡ Lastly, they are also connected by their common association with hare-lip, mental deficiency, and other anomalies of growth or development.

Clinical Characters; Ætiology.

The cause of the giant hand is, as a rule, unknown. It has been ascribed to a fall or blow,§ or other *injury*, though there is some reason to suspect that this is not always correct, but is sometimes to be attributed to that natural horror of an ætiological vacuum

* ‘Wien. klin. Rundschau,’ January 19th, 1905, S. 44.

† Sir G. M. Humphry, ‘New Sydenham Society Trans.,’ vol. clxxiii, p. 235.

‡ Kopal, ‘Prag. med. Wochenschr.,’ 1895, No. 33, S. 161.

§ J. Sabrazès C. Cabaunes, ‘Nouvelle Iconographie de la Salpêtrière,’ p. 343, September and October, 1899.

which exists in the minds of most people. In some cases the disease has apparently been due to parental *syphilis*, but without satisfactory evidence that local gigantism and other manifestations of syphilis have actually occurred together.

Age.—The giant hand is nearly always pre-natal in its origin, though as a rule it does not attain any great size until after birth. A few cases are recorded in which it was not noticed at birth. But some other forms of degenerative hyperplasia, particularly macroglossia, enlargement of the gums, and of the pudendum, are often of post-natal incidence.

Sex.—According to Professor Duplay* local gigantism of the hands or feet occurs most often in males. On the other hand, of Humphry's eleven patients with hyperplasia of the gums, nine were females.

Diagnosis.

Enlargements of the external parts sometimes go by the name of **elephantiasis**, but there can be no doubt that under this name there are often included diseases which differ widely in their pathology. True endemic elephantiasis is a disease primarily of the lymphatics, and is, according to Manson, as a rule, if not always, caused by the blockage of the lymph-stream by the eggs of the *filaria sanguinis hominis*. Evidently, therefore, it is a different disease from the idiopathic tissue overgrowth which constitutes the ordinary giant extremity.

Widely apart as these two diseases are, there is reason to believe that they are united by intermediate cases. At the one extremity we have tropical elephantiasis, which has a definite cause; is markedly endemic; affects, as a rule, the lower extremities or the genitals; generally begins in adult life; is never pre-natal; and consists, in the first place, in a purely lymphatic engorgement. At the other extreme is the giant growth proper, which has no known cause; has no particular geographical distribution; is generally pre-natal in origin; and is probably never, even in the first place, a lymphatic disease pure and simple, though the lymphatics may be very largely involved.

Yet there are cases which combine some of the main features of both. These may, or may not, have their origin in blockage of the lymphatics; may, or may not, occur endemically or at early periods

* 'Gazette Hébdom. de Méd. et de Chirurg.,' 1897, p. 529.

of life ; and the lymph stasis may, or may not, be accompanied by a decided increase in the growth of the surrounding fibrous tissue. In such indefinite cases the disease may begin as tropical elephantiasis, and subsequently give rise to such subsidiary overgrowth as to end in a condition indistinguishable from spontaneous giant growth. Or, on the other hand, true spontaneous and pre-natal giant growth may affect the lymphatics almost exclusively, so as exactly to simulate elephantiasis arabum. This occurred, for example, in Dr. Mainze's case,* in which a girl of four years of age, born in Germany, was affected with elephantiasis of the left upper extremity, both legs, the right foot and the external genitals. Here the age of the patient and the distribution of the disease indicated true local macrosomia of spontaneous origin, though it exactly simulated elephantiasis in its appearance and structure.

Tropical elephantiasis may occur in association with keloid,† an association which is of some significance when we remember that keloid is, like elephantiasis, much commoner in negroes than in whites, and is a form of scleroderma. Of still more significance is a case described by Friedberg,‡ in which true idiopathic giant growth of one lower extremity was associated with elephantiasis arabum in the other.

In a lecture given by Sir Jonathan Hutchinson before the London Polyclinic he points out that it is impossible to deny that non-filarial elephantiasis exists. Cases occur in England resembling those which are found in the tropics, and tropical cases may fail to show filariæ after careful search. A recurrent form of transitory "elephantoid fever" also occurs in both the temperate and the tropical forms. Its cause is obscure, though it is probably of bacterial origin, and denotes an increased vulnerability of the diseased tissue to attacks from the outside. Sir Jonathan Hutchinson suggests that the three chief causes of lymph blockage are (1) the pendulosity of the part ; (2) œdema due to fever ; and (3) some obscure disturbance of growth force.

There is, indeed, plenty of evidence to warrant the conclusion that though local gigantism begins without apparent cause, yet afterwards the dependent position of the parts, a blow or fall, gout or rheumatism, and especially any direct interference with the venous or lymphatic supply, such as varicose veins, thrombosis, glandular enlargement, or any other cause of venous or lymphatic

* 'Deutsche med. Wochenschr.,' Bd. xxv, 1899, S. 436.

† See cases pictured in the 'Polyclinic,' 1903, p. 288.

‡ 'Virchow's Archives,' 1867, Bd. xl, p. 353.

stasis,* may act as a secondary or aggravating reason for the complaint.

The real origin of the condition nevertheless consists in all cases of some "predisposition" or variation.

When the disease affects all four extremities it is prone to be mistaken for *acromegaly*, and this mistake is especially liable to occur if the lower jaw be involved at the same time. Such a case has been reported in one of the medical journals† by a most careful observer as an instance of *acromegaly*. But in this instance the commencement of the disease at birth, apparently in one foot, the irregularity of its course, the pronounced character of the deformity, and the absence of other symptoms of *acromegaly*, all tended to prove that the condition was due to local and not to general causes.

Heredity.

It is very unusual for conspicuous gigantism of hand or foot to occur in more than one member of the same family, if, indeed, such heredity ever occurs. Nevertheless there is possibly a hereditary form. Dr. Nonne has written an account‡ of the occurrence of "hereditary elephantiasis" in three successive generations. The grandmother was affected with "elephantiasis" of the legs, dating from birth. Her son came under Dr. Engel-Reimer's care with enlargement of the feet and legs, *including the bones*, and his sister showed a similar condition of the left foot and leg. Her first child was certified by Dr. O. Mayer to have "elephantiasis" of one leg; the second was acephalic, and had enlargement of the hands, feet, and legs, and the third and fourth showed the same disease in one leg and in both feet respectively. Dr. Nonne also mentions a case of Dr. Letissier's, in which "elephantiasis" appeared in three generations. Portraits are published of four of these patients.

The overgrowth apparently affected bone, muscle, and connective tissue, and was moderate in degree. In none of them was there any lengthening of the bone. One cannot therefore be certain that the disease was of the same nature as those gigantic growths in which the bone is extensively implicated. At the same time they cannot have been instances of ordinary tropical elephantiasis. Moreover,

* See Dr. T. E. Purdon's case, 'Brit. Med. Journ.,' 1883, vol. ii, p. 1281, in which elephantiasis started as a "white leg" after childbirth, and slowly increased for fifteen years, or up to the time at which the case was reported.

† 'Brit. Med. Journ.,' 1891, vol. ii, p. 188.

‡ 'Virchow's Archives,' F. 12, Bd. v, 1891, S. 189.

the occurrence of a pre-natal arrest of development (acephaly) in one of the cases is strongly suggestive of the enlargement being an abnormality of development of the same nature as those which constitute local spontaneous gigantism.

Dr. Stephen Mackenzie also writes* of a case occurring in a woman, aged 59 years, who had never been out of England. There was an elephantoid condition of various parts of the body, dating from the age of four years, and, in referring to it, he says that the father had swollen arms and legs from boyhood, and that of five brothers and sisters, four were affected in a similar way. It is possible that both this and the previous cases were instances of hereditary œdema, which is closely allied to macrosomia, if it be not, indeed, merely an hereditary form of that disease, and the distribution of the enlargement in this particular case is highly suggestive of ordinary local gigantism.

There is a plaster cast of a hand with a giant middle finger in the museum of King's College Hospital, of which Mr. Carling† states that it was taken from an individual who said that others of the same family possessed a similar malformation.

While it is very exceptional for giant growth of the hands or feet to exhibit direct hereditary transmission, it is not uncommon for this feature to show itself in an indirect manner through other malformations or stigmata with which it is associated (see p. 231).

But there can be no doubt that partial macrosomia of other parts than the hands and feet is sometimes hereditary. This may be said, for example, of hyperplasia of the gums. The occurrence of this disease in different members of the same family has been recorded by more than one authority.‡

Course.

Mr. Andersen, in his comprehensive article on "Congenital Hypertrophy," has said, "Its course is always in a certain sense *progressive*. Occasionally it appears to keep pace throughout with the general growth of the body, but in nearly all cases at some period abnormal growth strides in advance, so that the disproportion of the affected part to the rest of the body becomes more and more pronounced. Its progress may be uniform and continuous or terms

* 'Medical Society's Transactions,' 1887, vol. xi, p. 301.

† 'Med.-Chir. Trans.,' vol. xxviii, 1846, p. 342.

‡ Dr. Murray, 'Med.-Chir. Trans.,' vol. lvi, 1883, p. 235.

of slow increase or apparent arrest may be succeeded by new and rapid development.”*

In some instances of enlargement of slight degree, in which the overgrowth has been stationary for years, a sudden acceleration of growth has set in, suggestive of some radical change in the nature of the enlargement, such as we notice in other cases when a simple disorder of growth undergoes developmental changes. Thus in Mr. F. S. Eve’s patient† there was moderate enlargement of the left foot, which had remained stationary since birth, or rather had kept pace with the growth of the body. But at the age of twenty-four it underwent rapid increase in size, so that within eight months the foot had become so big and so heavy that the patient had difficulty in getting about. Moreover, during the last half of this period enlargement of the sole of right foot had set in. The right leg was amputated at its lower third, but the patient died from septic absorption the third day afterwards.

Another equally instructive case of similar delay is recorded by Gessler.‡ It is that of a lady, aged 62 years, who at birth had a thick right forearm, a supplementary finger on the right hand, and a large excrescence on the fourth finger of the left. The extra finger and the excrescence were both removed at the age of six weeks. At twenty-eight she suffered a contusion of the left elbow-joint, followed by complete ankylosis. Shortly afterwards inflammation and ankylosis of the left elbow occurred; then the forearms and hands, which had hitherto remained of the same relative size as at birth, began to grow, the thumbs and index-fingers and the right third, fourth, and fifth fingers all sharing in the increase. After a time it became necessary to amputate the fifth finger of the left hand, and from this time the growth increased more rapidly, but it was not until sixteen years had gone by that the third finger of both hands had attained such a size as to necessitate their removal.

Complications and Results.

Two concomitants or results of macrosomia are especially interesting.

One is the occurrence of *acute attacks of inflammation* mentioned in the descriptions of some cases. These are usually termed

* ‘St. Thomas’s Hospital Report,’ n.s., vol. xi, p. 168.

† ‘Trans. Path. Soc.,’ vol. xxxiv, 1883, p. 298.

‡ ‘Medicinisches Correspondenz-Blatt des Württembergischen ärztlichen Landesvereines,’ Stuttgart, June 6th, 1893 (Sajous’s Annual).

"erysipelas,"* though there is no evidence that the specific coccus of erysipelas is present. These attacks seem to last a few days, to be attended with fever, and to disappear as mysteriously as they came. Sometimes they are definitely the result of injury. Similar crises will presently be referred to when we come to the subjects of giant growths of the breast and of hereditary œdema. They are also a feature of tropical elephantiasis, when they go by the name of "elephantoid fever." In all probability they are bacterial in origin, and correspond with the acute attacks of inflammation which are prone to affect the large white or giant kidney and other organs in a state of degenerative hyperplasia. They signify a defect in the resisting capacity of the organ to microbial invasion.

The other concomitant is *ulceration*, which is also liable to take place from slight causes, or, to all appearances, from no cause at all, and is probably of the same significance as the febrile attacks just mentioned, though it is possible that in many cases it is solely degenerative.

Sometimes single ulcers are formed. They may be the result of injury, or of some other cause, as when they occur on the leg. Such a case is described by Professor Duplay.† In this a man with partial "hemi-hypertrophy" and diffuse nævoid growth showed ulceration of the enlarged leg as the result of a burn. The ulcer healed after prolonged treatment, but subsequently broke out again. Professor Duplay thought the ulcer was due to the loss of some "trophic" nerve influence, and in support of this view pointed out that there were alterations in the skin and its appendages, including thickening and pigmentation.

Sir Frederick Treves writes of a patient,‡ a girl, aged 20 years, in whom an ulcer appeared spontaneously on the outer side of a giant leg at its upper part.

Mr. F. S. Eve§ has also reported a case in which there was a single ulcer on the back of the metacarpal bone of the thumb of a giant hand. Amputation was performed through the lower half of the forearm, and subsequent examination of this ulcer by the microscope showed a near approach to malignancy in the tissue affected. In all probability certain cases of enlargement of the pudendum, brought to our notice by Dr. Matthews Duncan,|| and described by

* As in a case recorded by Mr. Hutchinson, 'Polyclinic,' 1903, p. 119.

† 'Gaz. Hébdom. Méd. et Chirurg.,' n.s., tome ii, 1897, p. 529.

‡ 'Brit. Med. Journ.,' 1884, vol. i, p. 1147.

§ 'Trans. Path. Soc.,' vol. xxxiv, 1883, p. 298.

|| 'Medical Times,' 1884, vol. ii, p. 672.

him as "lupus," were also of this nature. Dr. Thin, who examined microscopical sections of the ulcerated tissue, pronounced them to be histologically unlike ordinary lupus, "the morbid structure being diffused, and not occurring in nodules or tubercles." According to him the cells were either "white blood-cells or connective-tissue cells in various stages of development."

Ulceration does not by any means always affect the most marked cases. Indeed, a limb may be enormously enlarged, and no trace of ulceration be visible. On the other hand, there may be but slight enlargement with extensive ulceration; and when this occurs it is liable to be mistaken for some other disease, such as lupus or sarcoma. A good example of this ulceration is to be found in one of the bottles in the little Reading Pathological Museum. This is a hand of gigantic proportions, removed from a youth of ordinary stature by Mr. O. C. Maurice, and is dotted over with numerous round patches of shallow ulceration.

It is very difficult to find out what ultimately becomes of local giant growths. At the time they are reported, it is stated, as a rule, that they are continuing to increase, and the pictures given by Wittelhofer and others show to what enormous proportions they may attain. There is, it appears, rarely any limitation to the process of growth, however slow or discontinuous it may be, and there is no doubt that death results in some instances from the resultant debility.

But extremities do not always continue to increase in size, for cases are published in which growth has apparently been arrested or has even decreased,* though it may sometimes be questioned whether the arrest is only of a temporary nature, and due to the fluctuations or remissions to which reference has already been made.

Treatment.

Attempts have been made to stop the growth of giant extremities by means of *elastic compression*, and in some instances with a certain amount of success. This is of some effect where the enlargement is of the adipose type, as in the case mentioned by Holmes.† It is also said to have been successful when tried by Rerardes, though it did no good in a case of Dubreuil's.‡ Dr.

* See case of Mr. D'Arcy Power's (Harveian Society) 'Lancet,' 1893, vol. i, p. 1518.

† 'System of Surgery,' vol. iii, p. 799.

‡ Duplay, 'Gaz. Hébdom. de Méd. et de Chirurg.,' 1897, n.s., tome ii, p. 529.

Blackader* found Martin's bandage of very little use. As a rule, if improvement take place, it is but temporary, for the swelling returns when the compression is removed.†

A remedy of greater service is *ligature of the main artery* of the limb, which is recommended by Mr. Bryant.

Amputation has been resorted to in many cases, but not always with success, for death has sometimes resulted. Bleeding at the time of the operation may be profuse, and is also apt to come on secondarily. In Professor Duplay's case‡ a giant limb was amputated above the knee, but bleeding set in and proved very difficult to cope with. The hæmorrhage came not only from the stump, but also from the stomach, and proved fatal about forty-eight hours after the operation. In Dr. Blackader's patient, referred to above, the leg was amputated after compression had failed, with the result that death took place from excessive bleeding, also forty-eight hours afterwards. It is evident that *hæmorrhage* is greatly to be feared, for in a third case—that of Dr. Macgregor's§—the amputation of an enlarged lower extremity above the knee was attended by troublesome hæmorrhage, and was followed by excitement, vomiting, and hæmatemesis, ending in death at the same interval (forty-eight hours) after the operation.|| If we may judge from Mr. Eve's case,¶ *inflammation* is also prone to occur in the stump, and to be fatal.

Growth may recommence after removal. This has often been noticed when the tongue has been amputated for macroglossia, though wedges may sometimes be taken out with excellent results. In the latter event the organ not only heals well but afterwards shrivels down to its normal proportions. Recurrence is prone to take place after the removal of enlarged gums, so that Sir G. M. Humphry advises that part of the alveolar process should be taken away as well as the redundant gum. Instances have occurred in which single digits have been amputated on account of their bulk and neighbouring digits have afterwards taken on growth, though at the time of the operation they showed no sign of enlargement.** In V. Fischer's case amputation of a giant finger was followed

* 'Arch. Pediatrics,' vol. i, 1884, p. 626.

† See Dr. Stephen Mackenzie's case, 'Trans. Med. Soc.,' October 31st, 1887.

‡ 'Gaz. Hébdom. de Méd. et de Chirurg.,' n.s., tome ii, p. 529.

§ *Loc. cit.*

|| "Glasgow Med.-Chir. Soc.," 'Lancet,' 1896, vol. i, p. 994.

¶ 'Trans. Path. Soc.,' vol. xxxiv, 1883, p. 298.

** See Dr. Appleford's case, 'Hunterian Soc. Trans.,' 1897, part ii, p. 101.

within a few months by enlargement of the whole limb.* It is probable that the subsequent overgrowth was not directly caused by the amputation, but took place independently. Of similar significance are two instances of webbed finger,† in each of which division of the web was followed by giant growth of the conjoined fingers, though before the operation they did not look any bigger than usual.

Associations.

Local gigantism is frequently associated with other anomalies of growth or development, pre-natal or post-natal, occurring either in the same individual or in the same family.

Among the most common are nævi, mollusca fibrosa or other fibrous tumours, exostoses, lipomata, syndactyly, epilepsy, defective intelligence, strabismus and cleft palate.

Instances of associations with multiple disorders of the like nature have also been recorded. Among them are the following, namely, three cases, in children of the same family, of *mollusca fibrosa*, associated with one or more of the following conditions—*enlargement of the gums*, and of the *ends of the fingers and toes*, *connective-tissue tumours* of the scalp and other parts of the surface of the body, and various superficial affections of the skin.‡ Enlargement of the gums, according to Sir Jonathan Hutchinson, is often associated with some want of mental development, or with general dwarfism§ (infantilism?).

In the first three of the following examples defective mental development occurred in conjunction with giant hands or feet.

(1) *Elephantiasis telangiectoides* of the left lower extremity with *arrest of development* of the right (13·9 cm. shorter), *molluscum fibrosum* and *mental deficiency*.|| In this case the father and sister were also affected with mollusca.

(2) *Congenital elephantiasis* with *acephaly*.¶

(3) *Congenital and hereditary giant extremities* with *acephaly*.**

* Quoted by Anderson "Congenital Hypertrophy," 'St. Thomas's Hospital Reports,' N.S., vol. xi, 1882, p. 165.

† One in 'Guy's Hospital Gazette,' but not indexed.

‡ Dr. J. Murray, 'Med.-Chir. Trans.,' vol. lvi, 1883, p. 235.

§ 'Edinburgh Med. Journ.,' N.S., vol. i, No. 2, p. 117, February, 1897.

|| Dr. Wm. Calwell, 'Brit. Med. Journ.,' 1890, vol. i, p. 13.

¶ Dr. Nonne, 'Virchow's Archives,' 1881, Bd. cxxv, p. 189.

** Jacobsen, 'Virchow's Archives,' 1895, vol. cxxxix, p. 104.

(4) "*Hypertrophy*" of the right lower limb of a boy with *hypospadias*.*

(5) *Congenital enlargement of the mucous membrane* of the right side of the lower lip with *cleft palate*.† The same writer also says that Dr. Buck has recorded a case of *abnormal enlargement of the lower lip* from birth, in association with *næroid stain* of the chin and cheek.

(6) Marked *unilateral pseudo-hypertrophy* of the right side in association with "considerable increase in the size of the right optic thalamus by a *new growth*, the exact nature of which has yet to be determined" (Dr. A. N. Macgregor).

(7) *Enlargement of the left side* of the head and face, including the brain; *osseous growths* of the size of peas on the dura mater; *fibrous tumours* of the sclerotic; an *epulis*, the size of a pigeon's egg, on the left upper jaw, thick *villous growths* of the uterine mucosa, and a *large bony outgrowth* from the left patella.‡

(8) *Syringomyelia* with *giant extremities*.§

(9) Congenital "*hemi-hypertrophy*" associated with *nævus* of the same parts in a youth, aged 15 years, whose brother died from *hydrocephalus*.||

It should be noticed that in six of these nine cases the local hyperplasia existed in association with a local *defect* of development.

Structural Characters.

Macroscopically the chief distinguishing features of the giant extremity are its size, its deformity, its diversity of form, and the occasional presence of ulcers.

Of these four qualities perhaps the most significant is its variability. Hardly any two cases seem to be alike, though they may be roughly divided into those in which the tissues are involved more or less equally, and those in which the overgrowth is mainly of one tissue. The former approach the normal in structure, while the latter shade off into the lipomata, fibromata, and other tumours, or are indistinguishable from ichthyosis, scleroderma or other tissue degeneration. Owing to their diversity of structure some giant limbs, as we

* Dr. Hawthorne, 'Lancet,' 1902, vol. i, p. 671.

† Mr. Stephen Paget, 'Lancet,' 1892, vol. ii, p. 476.

‡ Mr. F. S. Eve, 'Trans. Path. Soc.,' vol. xxxiv, 1883, p. 298.

§ Holschewnikoff, 'Virchow's Archives,' 1890, F. xi, Bd. ix, S. 10.

|| Dr. F. Leith, 'Trans. Roy. Med.-Chir. Soc.,' vol. lxxv, 1892, p. 293.

have already seen, closely resemble the elephantoid limbs of tropical origin, and this happens more particularly when the lymphatics are implicated to any considerable extent. Some parts are more likely to have this appearance than others. This is especially true of the tongue, which is naturally honeycombed with lymphatics, and is therefore very prone to this form of enlargement. At other times macroglossia seems to be chiefly due to enlargement and sclerosis of

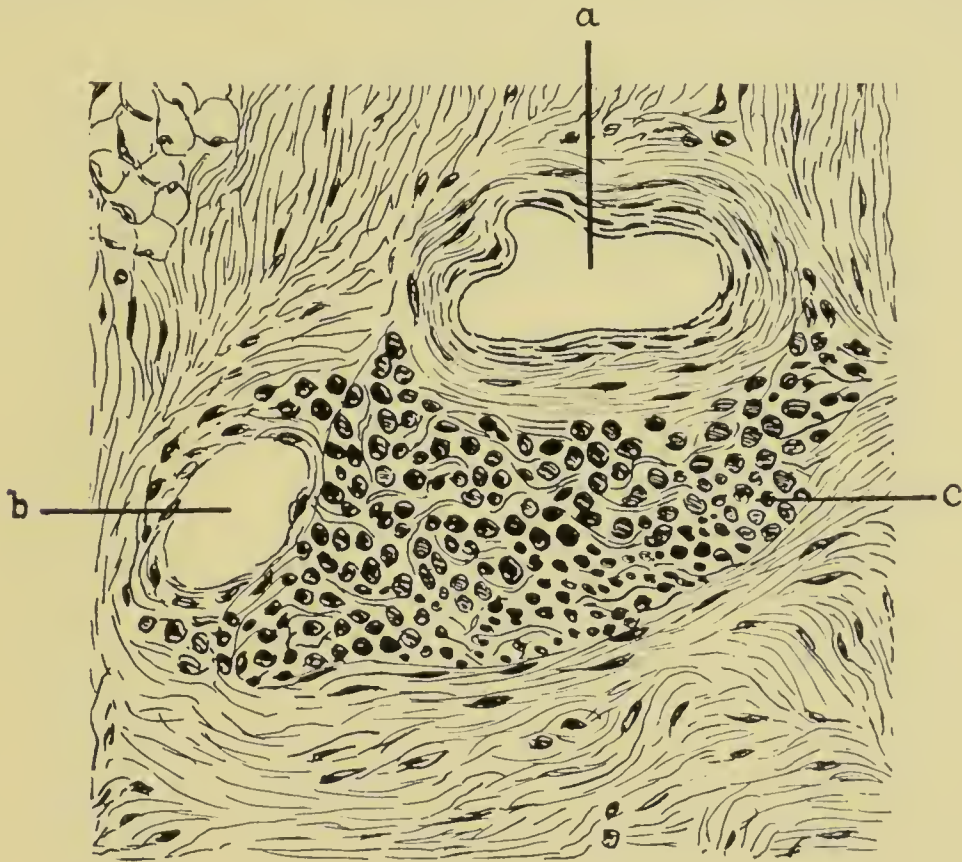


FIG. 1.—The section shows a vein (*a*) in a state of fibrous degeneration—sclerosis—an enlarged and open lymphatic (*b*), an excess of newly formed fibrous tissue, and, in the middle, a part of a degenerated sweat-gland (*c*). This last is made up of embryonic cells probably derived in part from gland-cells by denudation and in part from fibroblasts, mononuclears, lymphocytes, and cells of endothelial origin.

the blood-vessels, but it is a rare event for muscle or nerves (neurofibromatosis) to be the chief tissue at fault. At the same time it is probable that in many cases of macroglossia there is a certain amount of ichthyosis, of lymphangiectasis, of arterial sclerosis, and of muscular overgrowth.

Microscopical changes.—These, like the naked-eye appearances, vary greatly, and can perhaps best be described by giving some details of the structure of the giant hand of which mention has been

made (p. 229). The size and shape of this hand are very well shown in the adjoining figure.

All the tissues seem to be implicated, though not to the same degree. Thus the tissue most affected is that which forms the cutis vera and the areolar tissue immediately beneath it. Next in order come the bones, which are so softened and degenerated that

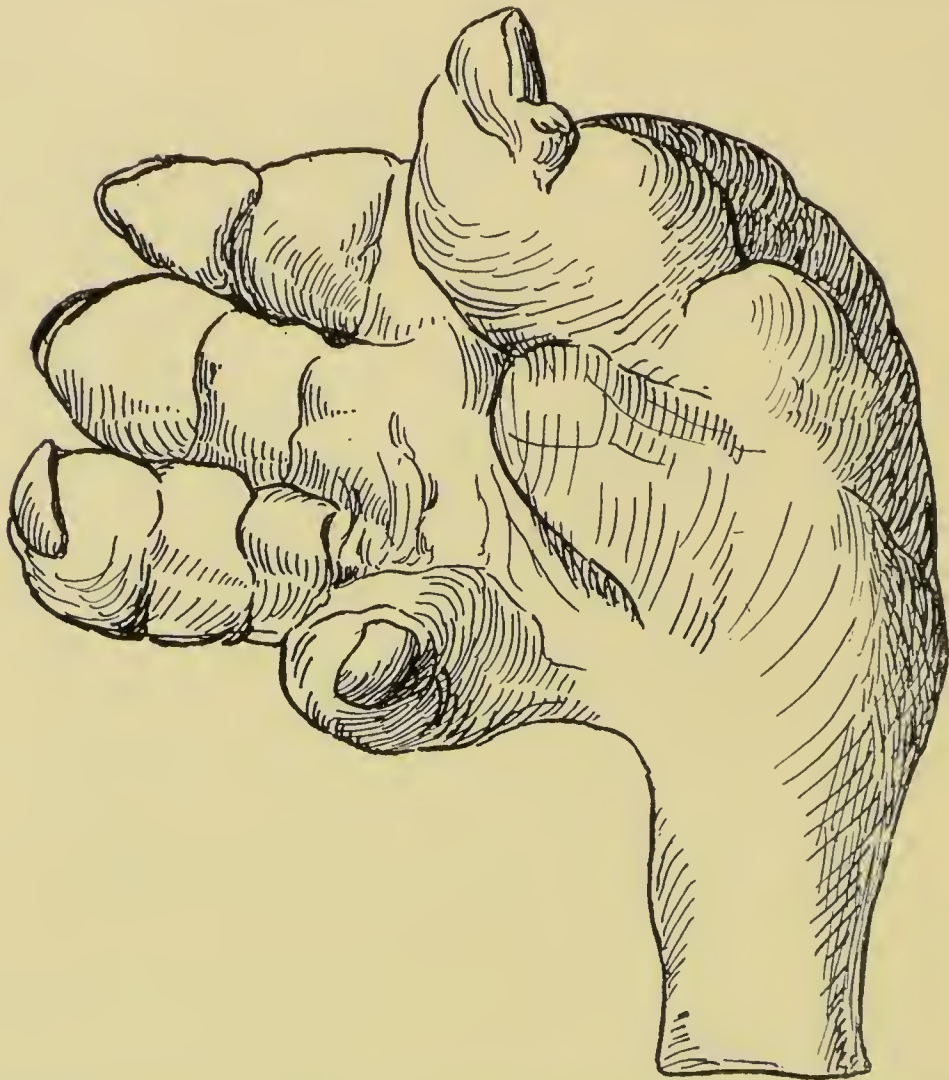


FIG. 2.—Giant hand. There is irregular overgrowth, giving rise to enlargement, deformity, and impairment of function, and constituting degenerative hyperplasia.

quantities of oil ooze out of them when they are cut into. The muscle perhaps is the least affected of all, though it is not easy to determine the state of the epidermal tissues, on account of the maceration to which they have been subjected. The lymphatic spaces are enlarged throughout and the arteries decidedly sclerosed. All three arterial coats are implicated, but the middle one chiefly.

The most conspicuous feature in all the sections examined, of

which some half dozen were taken from different parts, was the presence of islands of rounded, embryonic cells, which apparently proceeded from degeneration of the sweat-glands, for their distribution was confined to the area commonly affected by those glands. Moreover, ducts could be traced running down to them and no farther, and no normal sweat-glands were visible. At the same time the degeneration seemed to have been so complete that no intermediate stages could be detected. Delicate fibrils could, in many instances, be traced between the cells, giving them a remarkably sarcoma-like appearance; but, on the outskirts, many cells were undergoing transformation into connective tissue. This transformation had gone on to such an extent in some of the collections that only a few scattered round-cells seem to have been left, all the rest having changed into fibrous tissue. In other sections the razor had no doubt chanced to slice through the outskirts of a degenerated gland. The sweat-ducts, of which longitudinal sections were seen here and there on their way to the surface, were longer and straighter than usual, being no doubt stretched out by the growth of new subcutaneous tissue. Among them could be seen all degrees of transformation, from fairly normal epithelium to masses of proliferated rounded cells, resembling those formed by the degeneration of the glands.

It did not seem possible definitely to decide whether the new fibrous tissue arose out of the simplified gland-cells or whether it was solely the result of the renewed activity of the fibroblasts. Possibly the epithelial cells were first reduced to a rounded indifferent form, and these embryonic cells then proceeded to form connective tissue. Or, on the other hand, the new connective tissue may have had its origin solely in the phagocytes (fibroblasts, lymphocytes, endothelial elements) which had collected together for the purpose of dealing with the degenerated epithelium. Having accomplished their work it is probable that the phagocytes settle down into scar-tissue, and so account for the fibrosis.

The connective tissue everywhere was more than usually cellular. In the cutis vera there could in some places be detected groups of round-cells with no connective tissue between them, evidently formed by the proliferation, and probably the detachment of epithelial cells derived from the rete mucosum above. These occurred in the papillary layer, and sometimes, perhaps, a little deeper. The papillæ were very cellular and also extremely irregular, and the cells of the Malpighian layer dipped down long distances between them. The cells of the different layers of the epidermis,

moreover, could not clearly be differentiated, those of the mucosum being rounded and apparently devoid of prickle processes.

The *bone* was everywhere very oily, and showed signs of having undergone considerable absorption. There was no division into



FIG. 3.—A section showing periosteum (A) and bone (B) under a low power. The periosteum is thickened and is fibrous throughout. There is no shell of compact bone, but cancellous tissue ending abruptly (*a a*) against the non-cellular periosteum. The bone consists of a central calcified, more darkly stained (*b*), and a peripheral decalcified (*c*) portion. Between the spicules of bone the fatty, degenerated marrow crowds what is left of the cellular marrow against the periosteum (*d*) or the bony septa. Metacarpal bone.

compact and cancellous tissue, but it was coarse and porous throughout. The periosteum was thickened and vascular. Microscopically it was evident that there was no shell of compact bone, and that

the cancellous spaces were filled mainly with fat-cells interspersed among lymphoid tissue. In some places cartilage was found still undergoing changes resembling those which take place in the process of ossification, but in a much more coarse and irregular manner, so that no distinct columns of cells could be detected. At other places the bone already laid down was evidently becoming absorbed, for the borders of the spicules were decalcified, and here and there osteoclasts could be seen. In many places similar absorption of a calcified cartilage basis was proceeding, no true bone having been formed. Haversian systems, wherever they could be seen, were distorted or incomplete, and their central canals were excavated and filled with lymphoid tissue.

The collections of rounded cells just referred to have already been alluded to by Mr. F. S. Eve.* They probably account for the ulcerations noticed, though Mr. Eve thinks the ulceration is due to ingrowths of hypertrophied epithelium similar to that of cancer, but not cancerous.

Pathology.

Such facts as those just given tend to show that the disease represented by the giant hand is a degeneration. Moreover, though implicating the whole extremity or organ, this degenerative process either starts in some one structure or is very partial in its distribution, so as to give rise to much variety. The frequent presence of ulcers shows that the "nutrition" of the part is diminished, and a microscopical examination indicates that the whole process is due to a reduction of higher cell-elements to a lower level on the one hand and to a proliferation of low-class elements on the other. For example, the more specialised cells of the sweat-glands become reduced first to a rounded type of cells and then apparently to fibrous tissue. A similar change occurs in the bone-corpuscles, and the muscle-cells also undergo fibrous transformation. Hence quality everywhere gives place to quantity, and the structure of the whole organ is so deteriorated that it ceases to be of use. But although it sinks to a low position as a community of cells, it does not reach the level of the independent, single-celled organism and become cancerous. It still retains all the essential characters of an organ.

* 'Trans. Path. Soc.,' vol. xxxiv, 1883, p. 301.

Relations of Defective Development to Degenerative Hyperplasia.

Though each disorder of growth or development as a rule "breeds true," and overgrowth, or degeneration, or defect of one part is associated with a corresponding condition of another part, yet the two extremes sometimes occur together. Indeed, so often, comparatively speaking, does this association take place that one cannot doubt the existence of some intimate relation between them. Sometimes, for example, a defective or missing finger is associated with gigantism of other fingers or of the rest of the hand,* or a miniature hand is situated on the end of a limb which terminates abruptly in a fleshy lump of soft tissue, as if an amputation had taken place and an over-abundance of soft parts had been left, out of which some finger had afterwards sprouted.†

One concludes almost instinctively that in such cases some such process is at work as that which give rise to bosses on trees, or which causes pollarded willows to bulge at their extremities. But we cannot be too careful in accepting analogies of this sort. Their very familiarity is an element of danger, and tends to their adoption without proper examination. In this case, for instance, nothing seems more likely than that in a hand, with most of its digits dwarfed and others unnaturally big, the one irregularity should give rise to, or compensate for, the other.

But in reality nothing in animal physiology is, strictly speaking, comparable with the rising of the sap and the formation of adventitious buds in trees. There is no osmosis, capillary attraction, nor other force in the limb of a child such as would seek an outlet in other directions when its natural channel is obliterated. If the limb of an infant be cut off no bud-like processes ensue. And there is no reason to suppose that the tissues of the fœtus behave differently. Moreover, when there is an arrest of growth of a part and concurrent excessive growth on tumour formation, the latter often occurs, not only on the defective part, but also on other parts, or perhaps on the latter alone. Thus we find instances published of arrest of development of the ulna with exostoses of other parts of the body; of acephaly with giant growth of the lower extremities;

* Sir Jonathan Hutchinson, 'Edin. Med. Journ.,' n.s. i, 1897, p. 487; also 'New Sydenham Soc. Transl.,' vol. i, No. 5, p. 487.

† "Congenitale Missbildung des Vorderarmes," Dr. Cohen, 'Virchow's Archives,' 1894, Bd. cxxxvii, S. 387.

of ante-natal enlargement of the lower lip with cleft palate, and many others of a similar nature.

Such examples as these show that some other explanation must be sought, and the one which best covers all the facts is that the two extremes occur together, not because of any direct causal relation, but because they are examples of the same process of major variation, manifested in different ways, the one being a defect or immaturity and the other an excess or prematurity. In other words, they are correlated variations.

Relations of the Nervous System to the Developmental Diseases of the Extremities.

There is reason to believe that the nervous system and local infantilism and senilism are in some way connected. This seems to be proved by the following facts:

(1) There is a tendency for local developmental excesses and defects to be limited to certain nerve areas. This is sometimes the case with ichthyosis (Hutchinson), is common in ordinary circumscribed scleroderma, but is especially frequent in facial hemi-hyperplasia and hemi-atrophy. Each of the three great divisions of the fifth nerve may, in different cases, be picked out separately from the other two, or the whole of the nerve area may be affected at once. The occurrence of one-sided overgrowth or of complete hemi-atrophy of the body is also suggestive of some central nerve disturbance; and some of the irregular atrophies, such as that shown in Dr. Bury's case,* are almost more expressive of the same cause.

(2) Facial hemi-atrophy is occasionally preceded by persistent neuralgia, indicating some interference with the sensory branches of the fifth nerve. Indeed, in one celebrated instance† neuritis of the fifth nerve was actually demonstrated after death. We have somewhere seen it suggested that, when morphœa makes its appearance in these cases and pain ceases, it probably indicates that one disorder of the nerve has given place to another, or that, like neuralgia and herpes zoster, the pain and eruption are the different expressions of the same loss of nerve control.

In at least one case,‡ morphœa, limited to the area of the first and second branches of the fifth nerve, was accompanied by

* 'Brit. Med. Journ.,' 1887, vol. i, p. 458.

† Mendel's case, Virchow, 'Neurologisches Centralblatt,' 1888, 7. Jahrg., S. 401.

‡ Drs. Nettleship and Higgens, 'Brit. Med. Journ.,' 1883, vol. i, p. 961.

paralysis of the intra-ocular branches of the third, and it was pointed out that such cases are comparable with those of herpes of the fifth nerve, in which the third or other motor nerve is involved.

(3) The nutrition of sclerodermic areas is undoubtedly low, for they are prone to break down into ulcerated patches. Moreover, facial hemi-atrophy is sometimes associated with the formation of bullæ.

Such facts as these indicate the probability of the existence of some relation between the nervous system and the anomalies of growth or development, and it is but natural that this relation should be regarded as one of cause and effect.

Nevertheless, there are reasons for believing that the latter conception is incorrect.

Although the disease is sometimes limited to areas supplied by certain nerves or sets of nerves, there is still more often some irregularity of distribution, which completely spoils the utility of the case as an illustration of this theory.

The enlargement in most instances is by no means uniform, nor the symmetry complete. For example, the leg may be enormously enlarged, the arm and hand but slightly, if at all, or the face obviously and the scalp not at all; or with hemi-hyperplasia of such a description as this, there may exist a giant thumb or giant fingers on the smaller side of the body. In some patients the enlargement is partly on one side and partly on the other, and occurs quite irrespective of nerve supply. In a case of Mr. Pearce Gould's there was increased size of the right half of the cranium, brain, tongue and upper limb, as well as of the left side of the head and left lower extremity. Here, Mr. Gould remarks, there was "nothing to support the view that the size of the limb is dependent upon the development of the brain." In this, as in some other cases, the affection of one half of the brain seems to be a mere incident in the distribution of the disease.

In other cases *post-mortem* examination has failed to show any connection between local giant-growths and diseases of the nervous system. Thus Dr. Sophie Hornstein,* in writing of an infant who died with unilateral macrosomia, expressly states of the central nervous system that she "found no change which could be connected with the hypertrophy of the right side."

Then, again, there can be no question but that the facial enlargement is of the same nature as giant growth of the extre-

* 'Virchow's Archives,' 1893, Bd. cxxxiii, S. 440.

mities, and of similar hyperplasia of the gums and other localities. This is shown by the way in which the different varieties occur in the same subject, and also by their character and clinical features. If one is primarily a nerve disease so must the others be. But, as a matter of fact, there is no evidence that these other hyperplasias are of this nature.

Much importance is attached to the ulceration which takes place on the surface of some of the hyperplasias. But when we remember that we have to deal with a process which is considered to be, not an atrophy, but its opposite, it is difficult to see how ulceration can play any part in the process. We can understand that a bed-sore, a corneal ulcer or a perforating ulcer of the foot may eat into a part deprived of its nerve supply, but it is not easy to comprehend how a similar process can go on in a limb which has too much nerve supply and too much nutrition. The very name "trophic ulcer," usually given to these lesions, is a contradiction in terms. Moreover, the ulcers closely resemble those met with in the granulomata, and are suggestive of a new growth or degeneration rather than of the breaking down of normal tissue.

The correspondence in area of the lesion and of the nerve distribution does not necessarily imply that the developmental disorder is a disorder of nerves. It has been shown that there is a strong tendency for developmental diseases to affect certain physiological areas, such as the hands or feet. It so happens that half of the face and side of the head is supplied by one sensory nerve. And it is by no means improbable that the relation between them is, after all, one of association only, and not of direct cause and effect.

Progressive facial atrophy does not occur, as a rule, when the root ganglion of the fifth nerve is destroyed, though it may be supposed that any trophic fibres, if such there be, would be divided at the same time.

It is pretty evident that the nerve influence is a variable factor, and most likely plays only a subsidiary rôle. A nerve area is, in fact, a physiological area, for the part supplied by any one nerve is so supplied because the cells of that particular district are specially called upon to work harmoniously together. A patch of surface nerve supply is, indeed, as Hilton has shown, in intimate relation with the structures which lie beneath or otherwise act in conjunction with it. Such an area, quite apart from its nerve supply, is on the way to become an organ. Scleroderma, in fact, affects the face or certain parts of the face, not so much because it is in the district

of a particular nerve, but because that nerve marks the limits of an area partaking more or less of the nature of an organ.

Persistent Hereditary Œdema: Milroy's Disease.*

This disease was first described by Milroy in America in 1892. His record embraced six generations, including ninety-seven individuals, of whom twenty-two were affected. Meige (1898) recorded eight affected in four generations, H. D. Rolleston (1902) three in two generations; Hope and French (1908) thirteen out of forty-two persons in five generations. Besides these many isolated cases have been described.

The disorder is characterised by gradual painless, permanent swelling of the feet and legs, extending, at a jump, first to the knee, and sometimes to the groins, but no higher. The disease appears in both sexes, either before birth, or at some variable period of rising development, or definitely at puberty. It may continue gradually increasing for many years (in one case twenty-five years) without incident, and then become liable to acute attacks of pain, fever, with perhaps rigors and vomiting. These attacks last three or four days and spontaneously pass away, leaving no trace. They strongly remind one of the attacks of so-called inflammation, sometimes termed "erysipelas," which are recorded in some cases of local gigantism (tongue, hand, etc.), and of the "elephantoid fever" met with in elephantiasis, but Drs. Hope and French are inclined to regard them as of the nature of vasomotor neuroses. They compare the phenomena of the "acute attacks with those met with in Raynaud's disease, factitious urticaria, and angio-neurotic œdema," and see in them a very close resemblance.

We may venture to add yet another disease for comparison, and that is persistent hereditary jaundice. This disease, like persistent hereditary œdema, is either of pre-natal or of post-natal origin, is apparently spontaneous, hereditary, and above all, is liable to mysterious exacerbations attended with fever, with shivering, nausea and vomiting. These disappear in three or four days, leaving no after-effects. The disease, moreover, does not seem seriously to cripple the individual affected, and is not dangerous to life. It has intimate relations with a group of diseases of the spleen and liver.

* 'We are largely indebted to the article entitled "Persistent Hereditary Œdema of the Legs with Acute Exacerbations," by Drs. Hope and Herbert French, in the 'Quarterly Journal of Medicine,' 1908, vol. i, p. 312.

Milroy's disease is also prone to be associated with certain nerve disorders of a "degenerative type." Thus Drs. Hope and French draw attention to the occurrence of imbecility or weak intellect, fits, dipsomania, insanity in the family to which their cases belonged. Of all these associated disorders epilepsy seems to be the most common, and some analogy may perhaps be drawn between the "fits" which occur in epilepsy and the equally mysterious and spontaneous "acute attacks" of Milroy's disease. Similarities have also been noticed between this disease and the muscular dystrophies.

But when we attempt to trace out the relations of disease in this way we are soon entangled in a meshwork of interlacing morbid and semi-morbid conditions. The fact is that not only the diseases which have been mentioned, but many others, presently to be alluded to, are closely connected by ties of kinship. What is the exact position of hereditary œdema has not yet been determined, but there can be no doubt that it is a major variation.

II

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF THE CAVITY OF THE NOSE

Hypertrophic and atrophic rhinitis are excellent examples of major and minor variation. Hypertrophic rhinitis is a degenerative hyperplasia corresponding with scleroderma, and, like that disease, is prone to end in atrophy (atrophic rhinitis).

DISEASE of a type similar to that which contributes to the giant hand, scleroderma, or sclerema, affects those projections or extremities (turbinated bodies) which exist in the nose. Other parts of the nasal cavities and pharynx may be affected as well.

“**Hypertrophic**” **rhinitis** is, as a rule, of spontaneous occurrence, though it has also been attributed to syphilis and to chronic alcoholism. It is occasionally seen in brothers and sisters. All the constituents of the turbinated body, including the bone, may be implicated; or the disease may be almost confined to one tissue alone. Hence Mr. Wingrave,* as the result of his investigations, divided hypertrophic rhinitis into four varieties: (1) Cavernous or vascular; (2) mucoid; (3) lymphatic; (4) glandular. Moreover the outgrowth is very irregular, so that, in different cases, not only are these varieties mixed in all proportions, but one part of the turbinated body is often much bigger than another part, and polypoid or other tumours are apt to form on the diseased tissues. It is bilateral as a rule, but may affect one side only. Ulceration often takes place. Though the hyperplasia cannot be cured by any save mechanical or destructive processes, it is prone to undergo spontaneous wasting, and to turn into the atrophic variety.

Atrophic rhinitis may also apparently start *de novo*, and, when it does so, resembles the hypertrophic form in showing evidence of having some hereditary antecedent, in occasionally being set up by alcohol or syphilis, and in tending to affect all the structures in the turbinated bodies. The tissues undergo fibrous transformation or

* Lennox Browne, ‘The Throat and Nose,’ p. 572.

fibrosis. Ulcers are apt to appear, and from these ulcers, in rare instances, there may spring those semi-malignant tumours, the bleeding polypi of the nose.

From these characters it is evident that we have in hyperplastic rhinitis a disorder which cannot be distinguished in any essential particular from the giant hand, though in some respects it reminds us still more strongly of scleroderma. One of these is the way it recedes and gives place to the atrophic form. In this respect it is peculiarly like facial hyperplasia. Like the atrophic forms of these disorders, atrophic rhinitis may start as atrophy, implicating all the tissues, including the bone.

Biological Aspects.

Hypertrophic and atrophic rhinitis may be selected from among the disorders of organs hitherto dealt with as examples of discontinuous and continuous variations.

When any of these diseases occurs in a pronounced form without cause, and in more than one member of the same family, it must be regarded as an instance of regressive and *discontinuous variation*.

But nasal structures are often affected in a similar way, though to a less conspicuous degree, by bacterial infection or irritating gases (chlorine, formalin). In such cases there is, firstly, inflammation; and this inflammation (coryza) starts into activity another process—degeneration. Degeneration of this sort varies in degree, from true atrophic or hypertrophic rhinitis at one end of the scale, to slight hyperplasia or hypoplasia of a part of a turbinated bone at the other. These environmental conditions are of the nature of regressive *continuous variations*, and are usually recoverable if properly treated with inhalations, caustics, cautery, etc.

All these developmental disorders of the nasal organ are excellent examples of the rule that a degenerated organ or tissue is morbidly vulnerable to bacterial attacks, for it is well known that those who suffer from them are peculiarly liable to coryza, and, in advanced cases, the patient is constantly tormented with the discharge, crusts, and evil odours which spring from inveterate bacterial decomposition.

III

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF MUSCLE

Undergrowth or **under-development** may be local or general. The same may be said of **overgrowth**. The varieties of **degenerative hyperplasia** are muscular dystrophy, myotonia congenita, myositis fibrosa, myositis ossificans, and possibly myasthenia gravis. Muscular dystrophy is further sub-divided according to the muscles affected. All correspond in their origin, course, results, anatomy, and associations, with senilism affecting other organs. All are based on physiological precedents, and none deviates from the pattern set by normal old age, except in the direction of prematurity or excess.

Simple idiopathic under-development and undergrowth of muscle are met with both as general and as local affections.

General muscular emaciation, when not dependent on any definite cause, is usually combined with leanness, and its subjects are sometimes shown as living skeletons in variety shows. Perhaps the boy pictured by Sir Jonathan Hutchinson in the sixth volume, p. 209, of his 'Archives' is an instance of this condition. Sir Jonathan Hutchinson at first pronounced him to be an example of ordinary emaciation of extreme degree, but afterwards thought it more likely that he was affected with progressive muscular atrophy. But he was doubtful of this last diagnosis too, seeing that the boy showed no signs of paralysis. We have seen a similar case in an adult in a variety show. He was extremely thin, but his appetite and digestion were good, and his muscles showed no signs of degeneration. It is improbable that such a condition as this was due to defective development. In all probability the actual muscular fibres were normal, and the abnormality was an affair of growth only, and not of development. It is the antithesis to those cases of combined muscular overgrowth and obesity to which reference is made in the chapter dealing with obesity.

Single muscles are sometimes very defective in size or are altogether absent. As a rule, when such is the case, the anomaly is not noticed during life, because some adjacent muscle or part of a

muscle undergoes increase, and does the work of the absent or defective muscle.

Overgrowth.

This may be either general or local. Examples of extreme **general muscular overgrowth** are furnished by the celebrated Thos. Topham, who was studied by Desaguliers at the beginning of the last century, and in modern times, *inter alia*, by another celebrated strong man. These are undoubted instances of extraordinary muscular enlargement with corresponding increase in function. They are classed by Klebs* among the typical blastomata. He says that muscular "hypertrophy" is often hereditary, and regards it as an abnormality, and not a mere high degree of normal growth. He also observes that the electrical reactions of muscles so affected are not always normal.

True **local hyperplasia** or "hypertrophy" may take place, as in a case recorded by Fulda,† in which the majority of the neck muscles were decidedly bigger and stronger than usual, but the sternomastoids were normal. Many of the muscles of the back, arms, and abdomen were also affected. They reacted feebly to faradism, and in portions removed during life it was seen that the fibres were twice as big as usual, and that there was no increase of fibrous tissue.

Functional hyperplasia apparently also occurs as a first stage of degenerative hyperplasia.

Degenerative Hyperplasia and Senilism of Muscle; Varieties.

Five well-marked varieties of primary muscle degeneration can be made out. These are:

- (1) "Pseudo-hypertrophy."
- (2) "Atrophy."
- (3) "Myotonia congenita," or "Thomsen's disease."
- (4) "Myositis fibrosa."
- (5) "Myositis ossificans."

(1 and 2) Pseudo-hypertrophy of muscle and primary muscular wasting are included in the one term of *muscular dystrophy* (Erb). They are now recognised to be mere phases or variations of the same morbid process. Muscular dystrophy is itself divided into

* 'Die Allgemeine Pathologie,' Bd. ii, 1889, S. 556.

† 'Deutsches Archiv f. klin. Med.' Leipzig (unverified).

varieties or types, according to the particular part of the body affected. The chief are the peroneal, the juvenile or scapulo-humeral, facial, femoro-tibial, and the "distal myopathy" of Sir Wm. Gowers. These various types are curiously select, so that the disease usually repeats itself in the same form in different members of the same family, and, owing to this fact, some authorities have even expressed their opinion that the different varieties have a distinct pathology. But it is now recognised that intermediate and connecting forms are by no means infrequent.

Causation.

Dr. Warrington,* in discussing the peroneal type of muscular dystrophy, says that "some form of *toxæmia*, such as that of measles, has preceded the illness, and that Egger's† two cases had been workers in lead, and Hoffmann mentions *alcohol* and *syphilis*." But even if such blood states act as causal agents in a few instances, in by far the greater number no cause whatever can be found, except those indefinite circumstances which tend to produce general enfeeblement.

Heredity.—Muscular dystrophy is far more often a family disease than are similar affections of the extremities. Less frequently it is transmitted by direct heredity. Sir Wm. Gowers says that when atrophy occurs as a family disease it is never associated with pseudo-hypertrophy. An interesting feature of the heredity is that some "types" of dystrophy far more often occur in different members of the same family than do others. For instance, it has been noticed by Dr. Hammond that when the legs are affected first the disease is much more likely to be hereditary than when it begins in the small muscles of the hand.‡ In Herringham's case dystrophy of the peroneal type had been transmitted through five generations, or twenty-six individuals, the males alone being affected.

Age.—Unlike the excesses and defects of development which have already been mentioned, those of muscle are rarely pre-natal, but, as a rule, first show themselves in early childhood. They may, however, appear at any age before puberty, and cases have been reported of their first appearance at a still later age.

Erb divides the muscular dystrophies into two main groups.

* 'Lancet,' 1901, vol. ii, p. 1575.

† 'Archiv f. Psychiatrie und Nervenkrankheiten,' 1897, Bd. xxix, p. 400.

‡ Dr. Warrington, 'Lancet,' 1901, vol. ii, p. 1575.

In the first are those which occur early in life (infantile form), and are distinguished by hyperplasia.

In the second are the dystrophies of youth and manhood, which are distinguished by hypoplasia.

"The younger the patient when first attacked the more rapid and destructive is the course of the disease."*

Sex.—The disease is found chiefly in boys, apparently because of the far more important part played by the muscular system in males.

The *course* is tardy but progressive. It often becomes slower or remains stationary for a time, but only to hasten again later on.

Prognosis.—However chronic the process may be, the consequences are in all cases disastrous to the usefulness of the muscle, though, owing to the nature of the tissue affected, the disease is never directly fatal.

Treatment.—It follows that treatment is of little avail, though Erb is of opinion that good is sometimes done by the use of galvanism, Faradisation, massage, and attention to means of nutrition generally. No reliance can be placed upon drugs of any description.

Associations.—Progressive muscular dystrophy is well known to be often associated with pre-natal malformations. Some of these are of the brain or spinal cord, and have given rise to the supposition that the disease is not primarily a muscular lesion, but is consecutive to a nervous change. But, as a matter of fact, they are only casual, not causal, accompaniments. Moreover, malformations of other parts are sometimes met with, either in the same patient or in other members of his family.

Anatomy and Pathology.

It has been pointed out by Sir Wm. Gowers that the one constant element in the enlargement and wasting which distinguish muscular dystrophy is the change in the muscle-fibres themselves.† This change is one of degeneration, and is shown in the usual way. The muscle-fibres are either too big, or too little; there is molecular dissolution of the cell-protoplasm, and multiplication of nuclei. These alterations are accompanied by an invasion of lymphocytes, proliferation of connective-tissue cells, and the formation of bands of new fibrous tissue. It is noteworthy that the increase in fibrous tissue

* Erb, "Progressive Muscular Dystrophy," 'New Sydenham Soc. Transl.,' p. 264.

† 'Brit. Med. Journ.,' 1902, vol. ii, p. 89.

may be seen at a time when the molecular decay in the muscle-fibres has hardly begun, and this fibrous tissue is often very abundant. In this latter respect it differs from the fibrosis which sets in in normal old age, for the quantity of fibrosis then bears some relation to the degree of molecular disintegration, though the difference is, after all, one of degree rather than of kind.

Unlike corresponding hyperplasias of the extremities, the degenerative hyperplasia of muscle does not continue to increase indefinitely, but after a time the new connective tissue is absorbed, and a condition of degenerative atrophy results. It should be noticed that the muscle-fibres do not become smaller by mere strangulation and pressure, but undergo a process of molecular decay, identical with that which takes place in the atrophic form. Sometimes vacuoles appear in the degenerated fibres, and in extreme cases a cystic condition may result.

In some cases the disease seems to *begin in functional overgrowth* of the muscles, for, according to Sir William Ferrier,* Erb's juvenile form, which affects the muscles of the shoulder-girdle and upper arms, is not infrequently accompanied by "hypertrophy" of some muscles, though there is pseudo-hypertrophy of others. But there is reason to suppose that the enlargement of muscle-fibres sometimes seen is not the result of true overgrowth with excess of function, but of that form of overgrowth which comes with a loosening of the restraints of development and a return to an embryonic form.

Acute molecular changes have been noticed in the peripheral nerves, and changes have also been seen in the anterior horns of the spinal cord, but there is no ground for assuming that these are primary.

Everything goes to show that the disease is in the main a direct degeneration of muscle. When there is enlargement it is evidently due to degenerative hyperplasia, and when there is wasting it is sometimes consecutive to the hyperplasia and is sometimes primary, as in ordinary senilism. In this respect it resembles scleroderma, the cirrhoses of the liver and kidney, and the corresponding degenerations of the nasal organ.

Myotonia Congenita—Thomsen's Disease.

Thomsen's disease is essentially a pseudo-hypertrophy, for it gives rise to no increase in muscular strength. It is idiopathic, progres-

* 'Brit. Med. Journ.,' 1893, vol. ii, p. 721.

sive, often intermittent in course, of long duration, pernicious in its effects, and incurable. It differs from degenerative hyperplasia of ordinary type in the extreme frequency with which it occurs as a family disease, and in the marked increase in size of the muscle-fibres, without other microscopic evidences of degeneration, such as fatty changes or increase of fibrous tissue. What is the real difference between pathology of this disease and that of pseudo-hypertrophy of ordinary kind is not known, but that the two are related is extremely probable, not only because of the clinical characters which they have in common, but also from the fact that they may, according to Dr. Vigonroux, occur together in the same person. He has reported a well-founded case of Thomsen's disease* in which it was associated with pseudo-hypertrophic paralysis.

Weidmann records an instance of its association with epilepsy, and Pontoppidan describes a case in which it was associated with many degenerative conditions.†

It shows a tendency to occur more often in some localities than in others, for it is comparatively common in Scandinavia and Germany, and is exceedingly rare in America.

Structural changes.—Erb, and after him, Jacoby,‡ found enormous overgrowth of muscle-fibres with proliferation of nuclei, indistinctness of striation, a homogeneous appearance on transverse section, some vacuolation, and a slight increase of peri-mysium. The characters are suggestive of hyperplasia combined with a mild degree of degeneration.

Demme§ has recorded a case of hyperplasia of the muscles of the left half of the body only. The condition began immediately after birth, swallowing became difficult at the end of the second month, because of the enlargement of the left half of the tongue, and the child died a few weeks afterwards from insufficient food. The muscle-fibres were found to be unusually large in diameter, their transverse striæ were obliterated, and there were granular changes in the primitive fibrils. The condition therefore seems in some respects to have resembled that met with in myotonia congenita.

* 'Arch. de Neurologie,' November, 1884, Bd. viii, S. 272.

† Quoted by Dr. Jacoby, 'Keating's Cyclopaedia of the Diseases of Children,' vol. iv, p. 945.

‡ *Loc. cit.*, p. 946.

§ 'Archiv f. Kinderheilkunde,' 1894, Bd. xvii, S. 135; also 'Arch. of Pediatrics,' vol. ii, 1894, p. 321.

Myositis Fibrosa.

This is apparently a connecting link between muscular dystrophy and myositis ossificans. It occurs in children, causes extreme contraction of the muscles, many of which may be affected simultaneously. In reality the contraction does not seem to be so much a contraction of the muscle itself as of new connective tissue formed between its fibres. These latter undergo much fatty changes and wasting. Dr. F. E. Batten* believes that the disease is closely allied to myositis ossificans, and in his case noticed that the great toes were shorter than the second, third, and fourth toes.

Myositis Ossificans.

This also is a disease of early life, more common in males than in females. According to Drs. Weill and Nissim it has begun so early as a fortnight after birth, and evidences of its pre-natal occurrence have been noted. In fifteen out of forty-two cases it began within the first two years of life. Of the remaining twenty-seven some half-a-dozen first showed signs of the disease at from nineteen to thirty-two, but one case reported by Kronecker started at fifty-four.

The Teutonic seems to be much more often affected than other races. The disease has one very striking difference from ordinary fibrous myopathy; it is so seldom inherited that apparently there is, up to now, only one instance of heredity on record. In this, Dr. Burton Fanning's case,† the disease began at eight and was inherited from the father. All four limbs were almost fixed and the spine was rigid. It was noticed that the great toes were microdactylous.

Myositis ossificans is often *associated* with malformations of the digits.‡

Myositis ossificans is rarely due to injury. Its *course* is very variable. "It may progress very quickly, stiffening all the joints

* 'Trans. Clin. Soc. Lond.,' vol. xxxvii, 1903-4, p. 1.

† 'Lancet,' 1901, vol. i, p. 625.

‡ See Dr. W. P. Herringham's case, 'Trans. Clin. Soc.,' vol. xxix, p. 221, and vol. xxxii. In a patient of Drs. Crawford and Lockwood of Sheffield the ungual phalanges of the third and fourth toes of the left foot were absent, the metacarpal bone of the right hallux was much thickened and was fused with the first phalanx, and there was microdactyly of each thumb.

in a few years." In the patient of Drs. Weill and Nissim, the disease began acutely at the age of twenty with swelling, pain and fever, which prostrated him for three months, and then ceased for a time, only to recur later on. He had six attacks of this kind within five years, and then the disease had apparently come to an end, leaving the unfortunate man almost immobile and reduced to seeking the means of livelihood by exhibiting himself in variety shows. This intermittence in the course of the disease has also been noticed in many other cases.

In regard to its *anatomy*, Münchmeyer says that it begins with a proliferation of young cells in the interstitial connective tissue of the muscle, and these become transformed into fibrous tissue. Calcification then takes place at certain points, and is followed by true ossification. While this change is going on the muscle-fibres waste, losing their striation, and becoming transformed into connective tissue or bone.

The interpretation which has been put on these changes is that the intermuscular proliferation is primary and the result of inflammation, while the molecular degeneration of the muscle is secondary and due to the presence of new material.* But we shall afterwards see that a process of exactly similar nature may be observed in the nervous system in *tabes dorsalis*, and in the liver in *cirrhosis*, and in their case, too, a similar explanation has been given. We know now that in their case this view was incorrect, that in reality the process starts as a degeneration or simplification of the most highly organised constituents, and that the invasion of lymphocytes is secondary to it.

The physiological excuse for the disease is to be found in the intimate relations which exist between muscle and bone. Hence it is most common in males, whose muscular and skeletal systems are of comparatively high development, and is often combined with irregular thickening of the bone and with local outgrowths. It is probably correct to regard it as a pathological exaggeration of that tendency to calcification and ossification which is sometimes so conspicuous at the insertions of muscles, and is most obvious in the muscular. When we think that calcification is a feature of old age, and that muscles which are used inordinately, such as the adductor longus in horse riders, are prone to become calcified or ossified, it requires no great effort of the imagination to see in myositis ossificans a form of senilism based upon the changes which take place in normal senile degeneration.

* See M. de Witt, 'Amer. Journ. Med. Sciences,' vol. cxx, 1900, p. 295.

Myasthenia Gravis.

Drs. Klippel and Villaret* point out that myasthenia gravis behaves in many respects like the myopathies and myotonia congenita. Thus myasthenia occurs, in rare instances, as a family disease; in most cases the onset is during the second decade of life. The proximal muscles of the limbs are most affected. There may be conspicuous wasting of muscles, and the electrical reactions are quantitatively altered, not qualitatively. The rapid exhaustion of the muscles effected by Faradic shocks noted by Jolly (who first described this disease) as characteristic of myasthenia is occasionally a feature of muscular pseudo-hypertrophy, and of myotonia congenita. The authors also point to the fact that in both diseases the muscles are the parts affected, and not the nervous system, and that both are frequently associated with developmental anomalies.

They regard the three following diseases as different forms of myopathy :

- (1) Asthenic myopathy, feebleness without visible change in the muscles (myasthenia gravis).
- (2) Hypertrophic myopathy (Thomsen's disease).
- (3) Atrophic myopathy.

Dr. A. Knoblauch,† who remarks on the frequency with which pre-natal malformations and different kinds of tumours are found in the myasthenic, says that the muscles are often infiltrated with small round cells, and these cells may be collected together into patches, or surround the terminal blood-vessels. These cell collections were described by Weigert in 1901, and have been noticed by many other observers.

* 'Arch. Génér. de Med.,' 83 an., p. 353.

† 'Frankfurter Zeischrift f. Pathologie,' 1908, Bd. ii, S. 57.

IV

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF THE BREAST

Breasts of **defective growth or defective development** are peculiarly liable to become cancerous. **Overgrowth** as a rule begins when normal impulses of growth are most vigorous. **Senilism** occurs in two forms—degenerative hyperplasia and degenerative hypoplasia. The time of onset of the former, or giant breast, as well as its course, associations, and structure, are those characteristic of senility. The only treatment is by operation. Degenerative hypoplasia is distinguished by its near approach to normal senile degeneration. **Cystic disease** is either primary or secondary to fibrous or to single cell degeneration, and is a variety of degeneration.

So far the organs with which we have been dealing are either of very wide distribution or are not clearly differentiated from adjacent parts. But this cannot be said of the organ with which we are now concerned. The female breast is a collection of tissues specialised from a sebaceous gland (Mr. Roger Williams), provided with its own blood and nerve supply, and distinct from all the structures which surround it. It is a terminal part, a physiological area, and is under the control of special nerves. It is liable to many fluctuations of growth and development, and physiological hyperplasia and hypoplasia occur in it in their most pronounced forms. Under these circumstances it is but to be expected that all the anomalies of growth and development should be met with here in their extremes, and that they should, as a rule, be strictly limited to its substance.

I and II. Defective Growth and Defective Development.

The development of the breast may cease at any stage of its progress towards perfection, but it is probable that in many abnormally small breasts the anomaly is one of growth rather than of development.

The undeveloped or undergrown breast is of interest chiefly because of its liability to cancer, and this liability seems to be most evident when the breast is not in its usual place.

Mr. Roger Williams* has collected fifty instances of the occurrence of supernumerary breasts, and found that in 14 per cent. there were fibro-adenomata present, and that of 132 cases of cancer of the mammary region 9·8 per cent. had begun in supernumerary breasts.

Le Fort,† in an article on this subject, says that there are three varieties of supernumerary breasts—one in which the nipple occurs alone, a second in which there is nothing but the gland, and a third in which both are present together. As a rule, cancer takes place in the second of these varieties, and is rarely found in the other two.

Defective development of the breasts may either stand alone or be only part of an under-development of the whole genital system. In the former case the breasts may undergo no enlargement as a result of pregnancy,‡ so that there is complete absence of milk.

III. Overgrowth.

Simple overgrowth or so-called “hypertrophy” of the breast is said by some writers to be unknown.§ But this is undoubtedly not correct. Schüssler, for example, has described two cases of true “hypertrophy.”|| The gland was examined under the microscope, and nothing but an excessive growth of typical gland substance could be found. He says that the affection usually appears at puberty, first in one breast, and about six months afterwards in the other.

Zweifel¶ gives details of another case in a very thin woman, who had in the first place small breasts; but during her first pregnancy they enlarged to such an extent that when walking she was obliged to support them with her hands. The enlargement was solely of the gland substance, and resulted in a secretion of colostrum. Overgrowth of this sort is doubtless a morbid extreme of that which frequently exists physiologically as mere over-secretion of milk. Similar enlargement may apparently occur in the male and constitute one form of gynæcomastia.

Functional hyperplasia is very prone to end in connective tissue or degenerative hyperplasia, such as will now be referred to.

* ‘Journ. Anat. and Physiol.’ vol. xxv, 1891, pp. 250 and 253.

† ‘L’Echo Méd. du Nord,’ 1905, p. 366.

‡ Keim, ‘L’Obstét.’ May 15th, 1901 (‘Brit. Med. Journ.’ “Epitome”).

§ E. g. Speth, ‘Munich Aerztlich. Intel. Blatt.’ 1886, S. 242.

|| ‘Arch. klin. Chirurg.’ Bd. cxl, Heft 2.

¶ ‘Centralblatt für Gynäk.’ 1894, Bd. xviii, S. 1346.

IV. Presenile Degeneration or Senilism.

There are two forms of degeneration of the breast, both of which are met with in pronounced degree. One consists in that kind of excessive or premature development which corresponds with the giant hand, and seems, in the first place, to be an impulse of growth, but so excessive that it speedily merges into true degeneration. Like giant hands these huge breasts are on the boundary between excesses of growth and premature senility. They first occur under forty, at a time of life when growth is vigorous. According to Billroth they often begin during puberty.

The other form of premature degeneration is met with in the degenerating periods of breast life. It is a true primary degeneration without preliminary overgrowth, and though overgrowth does take place, it is not of the secretory cells as such, as in the giant breast, but of cells of low type, that is, of lymphocytes, of fibroblasts, and possibly of degenerated gland-cells.

A. Degenerative Hyperplasia: The Giant Breast.

This form of degeneration may occur in one breast only, or in both breasts; in the single, or in the married.

Cause.—As a rule, no cause can be discovered, and we have not even been able to find that these breasts are *hereditary*. Their appearance is largely determined by *sex* and *age*.

Sex.—Giant breasts occur usually in the female, but are not peculiar to that sex, for, as a matter of fact, some instances of enlarged male breasts (gynæcomastia) can hardly be separated from them, for the enlargement may be relatively quite as great. Moreover, the structure of these male breasts is very similar.

Age.—In the female these enlargements generally begin at about the time of the onset of puberty, but, according to Duplay,* they may also start between thirty and forty years of age. In short, they may be looked for either near the onset of sexual life or shortly before the sexual functions expire.

Course.—Their rate of increase is very variable. Most of them run a chronic course, extending over some years. As a rule, one breast is affected first and then the other. In rare instances the course is *acuta*, and is attended with fever and great debility. The organ may then grow so rapidly that obvious increase in size takes place in a single night. Their increase is, however, not regular,

* 'Gaz. Hébdom. de Méd. et de Chirurg.,' N. S., Tom. ii, p. 529.

but spasmodic, or by uncertain increments, and such accelerations may apparently be either spontaneous or due to some physiological impulse, especially pregnancy.

Associations.—The breast is sometimes enlarged in “hemi-hypertrophy” of the body, and a case* is reported of a monstrous growth of the left breast in a child who was also the subject of congenital *macroductyly*.

Mr. Marmaduke Sheild† saw a girl, aged 17 years, with hyperplasia of the left breast, two rudimentary nipples on the right breast, an imperforate vagina, and large clitoris. She had never menstruated, was of dull intellect, and had other symptoms of hermaphroditism.

Prognosis.—They may remain stationary for a great number of years (thirteen years, according to Schüssler), but may then continue to grow and destroy life by the anæmia, emaciation, and debility to which they give rise. Their *nutrition* is defective, so that abscesses are occasionally formed, or gangrene may occur, and if by any chance they should receive some injury, the sore which results heals very tardily. In Garcia’s case,‡ a Creole girl, aged 16 years, with breasts which hung down to her knees, and weighed about 12 kg. on the one side and 28 kg. on the other, was on one occasion dragged into the fire while leaning down to pick something up, with the result that extensive and deep ulcers were formed and refused to heal.

Anatomy.—Giant breasts vary widely in their structure. Some are soft throughout, and seem to be made up almost solely of gland-tissue with very little molecular degeneration or connective-tissue hyperplasia. But most of them are composed largely of connective tissue with wide, thick-walled lymph- and blood-vessels. The acini and their contained parenchyma are much wasted. Sometimes the skin is thick and hard, and there may, or may not, be enlargement of the nipple. The condition is variously described as one of “chronic fibrous mammitis,” “diffuse fibromatosis,” “adenomatosis,” or “hypertrophy,” according to the characters of the particular breast which happens to be examined.

The increase in size in some female breasts has been so enormous that the organs have weighed as much as 30 kg.,§ and have been insupportable burdens to their possessors. A case is reported in the

* Dr. Hahn, quoted by Dr. Jacobson, ‘Virchow’s Archives,’ 1895, F. xiii, Bd. ix, S. 104.

† ‘A Clinical Treatise on Diseases of the Breast,’ p. 30.

‡ ‘Pamphlet, “San Luis Potosi, 1900” (‘Medical Review’).

§ ‘Diseases of the Breast,’ Mr. Roger Williams, p. 85.

'Philosophical Transactions of the Royal Society' of 1669 by Dr. Weston,* in which death was directly due to their rapid and enormous increase in size. The left breast at puberty weighed 64 lb. (29·024 kg.), and the right 40 lb. (18·140 kg.). Many other instances of extraordinary enlargement have been published. Some of these breasts contain fibromata,† and in others the degeneration is so extensive that the breasts consist almost entirely of fibrous tissue or of fat. Sometimes cystic degeneration takes place.

Treatment.—Mr. Marmaduke Sheild‡ advocated the use of pressure and of elevation, combined with a dry, spare diet and the administration of iodides, and mentioned a case in which improvement set in apparently as the result of this method.

Iodide of potassium has been tried alone, but is of no use, even when given in mammoth doses. The only correct treatment consists in amputation so soon as the nature of the ailment is recognised.

Dr. Gersuny§ has apparently been the only surgeon who has amputated hyperplastic mammae during pregnancy. The patient, a Hungarian, was in the fourth month of pregnancy, and was rapidly becoming thinner, weaker, and more anæmic. The disease first showed itself at the beginning of the pregnancy. The operation lasted three and a half hours, and was rendered almost bloodless by elastic compression. Some of the blood-vessels were of the size of the little finger. The amputated breasts weighed 6 kg. and 6·5 kg. respectively. Their structure resembled that of a diffuse adenoma. The right was also cystic. There was a supernumerary breast correspondingly enlarged, and this showed simple overgrowth of normal gland elements.

B. Degenerative Hyperplasia.

Breasts which are of defective development are especially liable to degenerate. This is well shown in supernumerary breasts, which are, as a rule, not only small in size, but are useless, owing to molecular decay of their gland-cells, and to the excessive formation of connective tissue. Degeneration is also seen in the breasts of those who have passed the menopause, when it is a mere exaggeration of physiological senile decay, but it may also be found at any age. It is often cystic, or shades off by degrees into normal

* 'Anomalies and Curiosities of Medicine,' Gould and Pyle, p. 759.

† 'E. g. Dr. Warren's case ('Anomalies and Curiosities of Medicine,' p. 760).

‡ 'A Clinical Treatise on Diseases of the Breast,' p. 122.

§ 'Wien. klin. Wochenschr.,' 1901, Bd. xiv, S. 1255.

senile degeneration on the one hand, and into overgrowth and degenerative hyperplasia on the other. In breasts which have undergone those fibrotic changes, which are termed "mastitis," there is simplification of epithelium, so that each cell elongates, proliferates (Raymond Johnson), and ultimately helps in the formation of thick bands and tracts of fibrous tissue. New connective tissue is also made by the proliferation of connective-tissue cells, and apparently by lymphocytes. These have to all appearances found their way into the organ for the purposes of clearing away the effete parenchyma, and, having accomplished their work, finish their career by forming connective tissue.

Cystic disease.—This condition occurs near the termination of the life of the breast as an organ, and merges by all degrees of gradation into ordinary senile degeneration. It is often bilateral, and is sometimes associated with cancer. There may be cystic disease of one breast with scirrhus of the other;* or cystic disease of one breast may be removed by operation, and some years afterwards be followed by cancer of the other. In one such case† cancer had been present but had not been suspected, and it was not until a post-operative examination had been made of the cystic breast that the cancerous change stood revealed.

It has been pointed out by Brissaud‡ that in cystic disease three kinds of breast-tissue are found together, though they are ordinarily apart. These are—(1) gland which has not secreted at all, (2) lactating gland, and (3) atrophying gland.

There are two kinds of cystic disease—one in which the cysts are primary, both breasts being affected, and the other in which it is secondary to fibrosis, adenomatosis, or sarcomatosis.

In removing cystic disease it is important to take away the whole of it, for Reclus,§ in describing a form of micro-cystic disease, says that in one patient recurrence took place in the scar after amputation, owing to some of the cysts having been left behind. He says that Quena, and after him Delbet, found that this form of cystic disease is due to proliferation of the acinal epithelium followed by sclerosis. "The proliferated cells at first secrete a fluid and then disappear, leaving the acini dilated with fluid."

* Mr. Betham Robinson, 'Trans. Path. Soc.,' vol. xlvii, 1896, p. 205.

† Mr. N. W. Nunn, 'Trans. Path. Soc.,' vol. xli 1890, p. 224.

‡ See Dr. Trevelyan's paper, 'Brit. Med. Journ.,' 1890, vol. i, p. 549.

§ 'La Tribune Médicale,' 1905, p. 203.

SECTION II

The Fibrous or Prosenchymatous Group

I

INTRODUCTION

The term "fibrous" and "prosenchymatous" denotes superficial, not essential distinctions. The fibroses of the liver and of the kidneys are the most notorious examples, but similar degenerations of the arterial, nervous and sexual systems will also be examined.

Of the fibrous degenerations of organs, perhaps the best known are those which affect the liver and kidneys, and comprise the different forms of cirrhosis of the liver and of primary Bright's disease. The term "fibrous" or "prosenchymatous," though convenient, must not be accepted, however, as in any way denoting a natural division. It is useful for purposes of classification, but is distinctly artificial. Moreover, it is not always applicable. This is very well shown in the case of the kidney, where we have one variety of Bright's disease which renders it hard, tough, fibrous, granular and shrivelled, and another variety which renders it big, smooth and fatty. This latter is, indeed, so cellular, and so clearly, not solely prosenchymatous, that it has received the specific name of the "parenchymatous kidney."

It would be singular if the liver and the kidneys were exempt from the general rule that organs which ordinarily attain a certain pitch of development are also liable to come short of, or to exceed, their normal mean, and to fall into the extremes of defective development on the one hand or of premature old age on the other. Put in this way, we see that the occasional existence of these abnormalities of defect or excess is almost self-evident. Just as the heart, thyroid, brain, spleen, and, indeed, every other organ sometimes fail in development or become prematurely old, so also must the liver or the kidneys, though the rest of the body may be normal. More-

over, all sorts of gradations between these extremes must occur, so that we shall not only have imperfections starting in pre-natal, but also in post-natal life, sometimes giving rise to symptoms of great virulence, at others to much slighter symptoms, or, indeed, to no symptoms at all.

We have also remarked that an organ remaining in an infantile or juvenile state is peculiarly liable to become prematurely senile. We shall see that this rule holds good in respect to the kidneys. The same rule also accounts for many cases of premature senile degeneration of the nervous system, uterus, ovaries, testes, and thyroid gland. It must almost necessarily also apply to the liver, but in the case of that organ it cannot be said that such a sequence of events has yet been described.

II

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF THE LIVER.

UNDERGROWTH, OVERGROWTH, AND DEFECTIVE DEVELOPMENT OR INFANTILISM OF THE LIVER.

These almost undoubtedly occur, but have not as yet attracted special attention. Infantilism of the liver probably accounts for some cases of atrophic cirrhosis or of acute yellow atrophy.

(a) Undergrowth and Overgrowth of the Liver.

Undergrowth of the liver cannot as yet be differentiated from under-development, and the little that can be said on the subject is included in the chapter upon defective development.

Overgrowth has also attracted very little attention, yet there can be very little doubt of its existence. It must have come within the experience of many practitioners to have found the liver dulness extending beyond its natural limits without giving rise to a single indication of disease. Occasionally a part of a lobe or a whole lobe undergoes hyperplasia, but when this happens, it is usually to compensate for previous atrophy of the other lobe. An adventitious lobe may project downward and simulate a tumour. We have known a local overgrowth of this sort removed in mistake for an adenoma with disastrous results.

(b) Defective Development or Infantilism of the Liver.

Arrest of development of the whole liver is apparently only known as a pre-natal condition. The adult organ is sometimes found deformed as the result of imperfect growth or development of one of its lobes, but such a condition is of purely academic interest, for whatever detriment may ensue from the functional loss of this particular part is amply compensated for by the activity of the remainder. It is highly probable that there is such a patho-

logical condition as post-natal defective development of the liver, and that this is shown by acholia or some other symptom of disease, but the disorder has apparently not yet been described. We can, at any rate, find no account of it.

We have seen patients with symptoms not readily to be explained except by the hypothesis that the liver was permanently of defective development. Such patients are liable to so-called liver attacks on the slightest pretext. A little worry, a winter morning spent in a chilly room, a game of hockey, or a touch of influenza is enough to cause a break-down of the hepatic functions. The bowels become loose, the motions pale, the digestion impaired. At the same time the skin does not turn yellow, the colour of the urine is not heightened, and there is no furred tongue nor metallic taste in the mouth. On percussing the liver region its area of dulness is slightly diminished. We have known symptoms of this sort last for weeks at a stretch, yielding to none of the remedies usually given in such cases, but, as a rule, slowly subsiding until the diminished liver dulness and some occasional deficiency of bile in the stools are all that is left to indicate what is amiss.

III

PREMATURE SENILITY OR SENILISM OF THE LIVER— CIRRHOSIS

Cirrhosis: The *varieties* of cirrhosis are numerous. They may be classified under two main divisions—those of hyperplasic and those of hypoplastic type. They are determined by the seat of origin, mode of production, age, and course. Cirrhosis is apparently sometimes consecutive to defective development. *Ætiology:* Hypertrophic cirrhosis is usually spontaneous; atrophic cirrhosis the result of irritation, alcohol being the most common irritant. *Sex:* Males are more often affected than females. Cirrhosis occurs in other *mammalia*. *Age* determines four varieties—viz. the juvenile or hereditary form of hypertrophic cirrhosis, the ordinary hypertrophic cirrhosis of early adult life, the atrophic form of middle age, and the atrophic form of old age. The *course* is progressive but interrupted. The most hopeful *treatment* is by operation. *Acute yellow atrophy* is probably an acute form of cirrhosis. The cirrhoses are *associated* with chronic Bright's disease, arterial sclerosis, fibrosis of the pancreas, and similar degenerations of other organs. The anatomy of the different forms of cirrhosis is fundamentally alike. All are characterised by retrogressive metamorphosis of gland-cells with increase of phagocytic cells and their transformation into fibrous tissue. The characters of hypertrophic cirrhosis denote a *major variation*, and those of atrophic cirrhosis a *minor variation*. Cirrhosis, being a degeneration of the organ as a whole, predisposes to degeneration of the cells in their individual capacity, as cancers. Summary and conclusions.

Varieties.

THE old division of cirrhosis into atrophic and hypertrophic is now known to be inadequate. The forms of cirrhosis are not two, but many. They may be classified according to their seat of origin, their mode of production, the age of the individual affected, and the rate of progress of the disease.

If we classify cirrhosis according to its *seat of origin* we recognise many different forms, each of which is founded upon the locality of the cirrhosis.

Thus, in the first place, we have two prime divisions of portal and biliary cirrhosis, according as the seat of fibrosis is about the ramifications of the portal vein or of the bile-ducts respectively.

In addition to these the position of the fibrosis may be determined by its commencement in the arterial coats, in the capsule, or around the individual cells. Different kinds may be more or less mixed, so that we have monolobular fibrosis in one place, multilobular in another, and pericellular in a third.

Varieties are founded not only upon the distribution of the fibrosis in the liver, but also upon some concomitant abnormality of the spleen or skin. Hence biliary cirrhosis has been subdivided by Dr. H. D. Rolleston into (among others)—

(a) The hypertrophic liver of Hanot's type, in which liver and spleen are both enlarged, especially the liver, constituting the "megalosplenic" form.

(b) Gilbert and Fournier's type of the "hypermegalosplenic" form in which the spleen is enlarged to a greater extent than the liver.

(c) The "microsplenic" form of Gilbert and Casteigne, in which the spleen is little if at all enlarged.

In addition there is a cirrhosis of which cancer is believed to be either cause or concomitant,* but may be secondary.†

Even these do not exhaust the list, for some of the different kinds may be mixed, or the cirrhosis may be mono- or multilobular in different parts of the same liver.‡ Moreover, there is no line of demarcation between one form and another. The distinctions "hold good with regard to typical cases only. Cases occur which show a combination of the characters of recognised varieties" (Hale White).

The same is true when we attempt to classify cirrhosis according to its *mode of production*. Though atrophic cirrhosis is, as a rule, the form produced by alcohol, yet alcoholic hypertrophic cirrhosis is described by Hanot and Gilbert§ and by Price.||

The cirrhosis of congenital syphilis, of acquired syphilis, of tubercle or of heart disease, though usually different from other varieties, may, in special cases, simulate the alcoholic and the idiopathic cirrhoses.

Then there are certain forms of cirrhosis which are almost always due to syphilis. One of them is the common nodular or partial form (tertiary syphilis), in which the fibrosis is consecutive to more

* "Epithélioma Trabéculaire" of Hanot and Gilbert, 'Études sur les maladies du foie,' p. 41, 1880.

† H. D. Rolleston, 'Trans. Path. Soc.,' vol. xxxiii, p. 172.

‡ Dr. Kretz, 'Brit. Med. Journ.,' 1905, vol. i, p. 1503.

§ 'Archiv. générales de Méd.,' vol. clxvi, 1890, p. 250.

|| 'Guy's Hosp. Reports,' vol. xlii, 1884, p. 295.

or less huge collection of embryonic cells (gummata). Another is the unicellular form which is seen in young infants, and is then almost invariably the result of congenital syphilis. The third is a kind of non-alcoholic atrophic cirrhosis which occurs between the years of eight and eighteen, is characterised by an extreme degree of fibrosis, and is also a parasymphilitic affection.* Dr. Adami,† of New York, says that congenital syphilis may take any one of four forms, to wit, ordinary gummata, miliary gummata, a mixture of these with general fibrosis, or general atrophic cirrhosis.

The *modifications produced by age* will be referred to under the head of causation.

Cirrhosis may also be classified according to the *rapidity of its course*. It may last for many years, or, on the other hand, may be fatal within a few months. This latter is the “*acnte*” cirrhosis of the liver or “*icterus gravis*” of Koerner.‡ Professor Eichhorst§ tells of an instance in which a man was ill for only two weeks before death; but, of course, in this, as in other cases, no one can say how long the disease had been latent.

Finally, acute yellow atrophy is possibly no more than ordinary cirrhosis modified by the rapidity of its course.

Cirrhosis Consecutive to Defective Development of the Liver.

Judging from what takes place in other organs, such as the spleen and kidneys, it is highly probable that much of the cirrhosis which occurs, at any rate during progressive development, is preceded by defective development. At first sight such a statement as this does not seem capable of proof, seeing that the liver is so buried in the somatic cavity that it can only be examined in a perfunctory and unsatisfactory manner.

Nevertheless, we have good reasons to suspect that cirrhosis is occasionally consecutive to infantilism.

In the first place we have to account for the fact that cirrhosis sometimes occurs in children without the slightest discoverable cause. This, by itself, is sufficient to lead us to infer that there is some antecedent condition paving the way for the fibrosis. Enough has been said in the first part of this book to show that nothing

* Dr. Lazarus-Barlow, ‘Trans. Path. Soc.,’ vol. 1, p. 146.

† ‘New York Med. Journ.,’ 1899, vol. lxix, p. 549.

‡ ‘Deutsch. Archiv f. klin. Med.,’ vol. xlii, 1888, p. 615.

§ ‘Virchow’s Archiv.,’ Bd. cxlviii, 1897, S. 339.

could be more likely to facilitate this transformation than defective development.

In support of this view is the fact that when some of these juvenile cases of cirrhosis undergo *post-mortem* examination the liver is found to be unexpectedly small. As a rule the cirrhosis is of the biliary kind, but instead of the usual enlargement the organ does not exceed its normal bulk. In other cases not only is the liver not "hypertrophic" but is actually diminished in size. In fact "atrophic biliary cirrhosis"* is a recognised variety. Possibly, of course, in some instances so described the liver was at one time too big, and became small by subsequent contraction of its fibrous tissue. But this explanation does not apply to all, for some have been noticed to be small from an early stage of their existence. It seems much more likely that the liver was small and infantile in the first place, and that the biliary cirrhotic process caused, as usual, an increase, and not a decrease, in size, but not to such an extent as to give rise to actual enlargement of the liver.

Clinical.

Causation.

The chief cause of atrophic cirrhosis of the liver is *alcohol*, and alcohol also apparently accounts for some cases of hypertrophic cirrhosis and of acute yellow atrophy. But it is only now and again that the excessive drinker acquires cirrhosis of the liver. Dr. Norman Kerr† has stated that out of fourteen cases in which alcohol was taken in such an amount as to produce fatal neuritis the liver was cirrhotic in only three,‡ and Dr. Peters§ found that no more than four or five out of seventy patients who died from excessive spirit drinking were affected with cirrhosis. Regarding the same question from another aspect, Pel, of Amsterdam,|| finds that abuse of alcohol accounts for only about one third of his cases, and that the heaviest drinkers escape.

These figures, after all, only express that which every physician knows, to wit, that cirrhosis of the liver in hard drinkers is the

* Lereboullet, "Les cirrhoses biliaires," 'Thèse Paris,' No. 180, 1902.

† 'Med. Chronicle,' vol. iv, 1896, p. 315.

‡ This statement is to be discounted by the fact that it is now known that neuritis is nearly always due to the contamination of alcoholic drinks with arsenic.

§ Dr. Payne, 'Brit. Med. Journ.,' 1888, vol. ii, p. 1327.

|| 'Die Krankheiten der Leber,' etc., 1909.

exception and not the rule. They show that there is some other factor at work besides alcohol, even in alcoholic cases. They indicate that in certain people there is a special "predisposition" to the incidence of this disease, and that without that predisposition no cirrhosis can exist.

There has been some discussion as to the way in which alcohol gives rise to cirrhosis.

Possibly it is by means of a direct irritative action upon the liver tissue, aided, perhaps, by the more roundabout, depressing effect of the drug upon the vaso-motor mechanism. That the former explanation is not improbable seems to be indicated by the fact that mechanical *irritants* are apparently capable of originating cirrhosis. Rolleston,* quoting Adami, Lancereaux, and Welch, shows that particles of carbon, or of stone, which have set up fibroid degeneration of the lungs, have, to all appearance, at the same time produced corresponding fibrosis of the liver.

Arsenic or silver, moreover, when taken medicinally for long periods of time, has apparently caused cirrhosis. Lead, however, has no such effect clinically, though Lafitte has produced cirrhosis experimentally by means of this poison.

It is, perhaps, on account of its irritant action that the artificial constriction of the liver by tight lacing is sometimes associated with cirrhosis. That there is some relation between them is suggested by the fact that the fibrosis may be confined to the constricted part.

Influence of Sex, Zoological Distribution, Age, Heredity.

Sex.—Males are more often affected than females, the proportion, according to Rolleston, being as 374 males to 134 females.

Zoological distribution.—Prof. Wallery says that typical gin-drinkers' liver is sometimes found in the bodies of young bullocks, and Profs. Coats and Greenfield have seen the disease in cats.† It has also been noticed in various other animals, and, as a rule, under conditions which put the possible influence of alcohol entirely out of the question.

Age.—Four sorts of cirrhosis can be distinguished if our criterion be that of age. These are (1) the *juvenile* or *hereditary*, (2) the ordinary *hypertrophic* or *early adult*, commonest between twenty and

* 'Diseases of the Liver,' p. 185.

† 'Brit. Med. Journ.,' 1901, vol. i, p. 1502.

thirty; (3) the *middle age* or *atrophic* cirrhosis, which usually occurs around about forty-eight; and (4) the *old age* form.

As in the case of other diseases, the distinguishing feature of each of these four is the heredity which characterises the first, the hepatic overgrowth which distinguishes the second, the hepatic wasting, which is such a marked feature of the third, and the slightness, or even absence, of symptoms of the fourth.

(1) ***The cirrhoses of childhood.***—"Idiopathic" cirrhosis of the liver may be either pre-natal, or post-natal and show itself in the early years after birth.*

Dr. Howard,† as the result of observations on sixty-one cases of cirrhosis in children, found that there was a history of alcohol in only ten, and that it was definitely stated to be absent in forty-seven. Syphilis was present in seven and absent in twenty-nine. In two the kidneys also were fibrous, and in two others three organs had undergone interstitial fibrous alteration. In six out of fifty-seven the disease appeared to be the outcome of "a general tendency to fibrosis." In twenty-four of the fifty-seven the spleen was abnormally large, in two of them large and tough.

When it begins in childhood cirrhosis usually takes the hypertrophic or biliary form, and, far more often than in the adult, has no obvious cause.

Again, cirrhosis of infancy and childhood is, according to Wills,‡ Rotch,§ and other observers, much *more rapid in its course* than is the cirrhosis of adult life. According to the former, it usually terminates within a year of the onset of symptoms.

In children cirrhosis more often shows *hereditary tendencies* than it does in adults.

It is very doubtful whether atrophic cirrhosis is ever inherited. Dr. Rolleston|| says that it "is not a "family" disease or one that tends to recur in members of the same family; in this way it contrasts with hypertrophic biliary cirrhosis which often attacks several members of the same family. In a few instances several adults may die of alcoholic cirrhosis, probably from a family failing towards alcoholism. In children the death of two or more members

* Stack, "Hepatic Cirrhosis in Children (under twelve)," 'Practitioner,' 1892, vol. xlviii, p. 186. He found five cases in which cirrhosis occurred before the age of one month.

† 'Amer. Journ. Med. Sciences,' vol. xciv, 1887, p. 350.

‡ "Cirrhosis of the Liver in Infancy and Childhood," 'Pediatrics,' vol. xiii, 1902, p. 208.

§ *Ibid.*, vol. iv, p. 839.

|| "Diseases of the liver," p. 181.

of the same family from multilobular cirrhosis is more often met with. This may depend on hereditary influences, syphilis disposing the organs to the incidence of ordinary cirrhosis—parasyphilitic cirrhosis.” *Biliary cirrhosis* is far more often hereditary than portal cirrhosis. Dr. Ormerod,* in an article on “Cirrhosis of the liver in a boy with obscure and fatal nerve symptoms,” mentions that Professor Homen has seen a similar conjunction of disease in three members (aged twelve, twenty, and twenty-one years) of the same family. In both Dr. Ormerod’s and Professor Homen’s cases degenerative lesions were found in the neighbourhood of the lenticular nuclei. The former also says that Dr. Gee had seen a similar case in a boy of thirteen, in whom, however, no nerve lesions were found after death. Dr. Buzzard and Sir Wm. Gowers have met with similar nerve disturbance occurring as a family disease apart from cirrhosis.

A good instance of heredity is given by Dr. Gordon† in an infant of fourteen months at the time of its death. It was the third of a family of four. Both of its parents were healthy, and there was no reason to suspect the influence of alcohol or of syphilis. The second child was affected with cirrhosis almost simultaneously, the disease running a similar course and ending in death within six months. The presence of cirrhosis was proved by *post-mortem* examinations.‡

Still another instance is recorded by Professor Osler, who has seen two brothers affected with biliary cirrhosis at the same time, and Dr. Rolleston say that in a family, referred to by Boinet, the father and two children suffered from hypertrophic biliary cirrhosis, while three other children had enlarged spleens.

Dr. Howard,§ in the paper already quoted, gives an account of uncomplicated cirrhosis of the liver in a girl of nine and in her brother of eight years of age.

Dr. Rolleston,|| who mentions most of the above cases of heredity, quotes Finlayson¶ and Dreschfeld,** and refers more particularly to a peculiar form of hereditary cirrhosis occurring among the children of Brahmins around Calcutta. This, which is described by Dr. J.

* ‘St. Bartholomew’s Hosp. Reports,’ vol. xxvi, 1891, p. 57.

† ‘Med.-Chir. Trans.’ (unverified).

‡ Dr. James, ‘Brit. Med. Journ.,’ 1902, vol. i, p. 619; also (three children) Hasenclever, ‘Berlin. klin. Wochenschr.,’ Bd. xxxv, 1898, S. 997.

§ ‘Amer. Journ. of Med. Sciences,’ vol. xciv, 1887, p. 350.

|| ‘Diseases of the Liver,’ p. 309

¶ ‘Glasgow Hosp. Reports,’ vol. ii, 1899, p. 39.

** ‘Med. Chronicle,’ vol. v, N.S., p. 19, 1896.

B. Gibbons and others, is intercellular and perilobular and occurs when the children are about eight months old. "No less than fourteen children of the same parents have died of it one after the other." Its cause is obscure. It has been attributed to the dry peppery diet of the mother. Sir Jonathan Hutchinson* says that all suggestion of alcoholic causation may be at once dismissed.

The hereditary cases are probably, as a rule, instances of Hanot's splenomegalic form of hypertrophic cirrhosis.

Course.

Owing to the fact that ordinary atrophic cirrhosis of the liver is latent for the greater part of its existence, and as a rule only becomes manifest shortly before death, it is not easy to say what sort of course it runs. Cirrhosis in general, as has already been said, makes quicker progress during infancy and childhood than during adult life.† It must be remembered that inasmuch as the cirrhosis of early life is biliary as a rule, it is usually detected much more early than is the small form because of the liver enlargement, and of the jaundice which goes with it. Now this jaundice, in particular, makes it possible to recognise the course of the disease, for it may be inferred that the depth of the jaundice is some criterion of its gravity. Dr. Rolleston says of this pigmentation that "it is slight at first, and becomes more marked as the disease progresses; it is permanent, but varies in degree, being intensified at intervals when exacerbations in the disease occur; after these crises it recedes."‡ Dr. Rolleston also says that these exacerbations coincide with increase in other symptoms; that they are like those seen in pernicious anæmia and in Addison's disease; and that the enlargement of the liver is generally progressive, but varies from time to time, first advancing and then receding.

Treatment.

The treatment§ of cirrhosis of the liver by operation was first advocated by Dr. Drummond, of Newcastle. In 1896 a paper was published in the 'British Medical Journal' (September 19th), giving an

* 'Polyclinic,' 1905, p. 264.

† See Wills, "Cirrhosis of the Liver in Infancy and Childhood," 'Pediatrics,' vol. xiii, 1902, p. 208.

‡ 'Encyclopedia Medica,' vol. vi, p. 499.

§ This historical summary is taken from 'Brit. Med. Journ.,' 1905, vol. ii, p. 892.

account of two cases of ascites which had been operated on by Mr. Rutherford Morison, at Dr. Drummond's suggestion. Only one of these subsequently turned out to be due to cirrhosis, and the operation was successful. Two years later, Talma,* acting independently, recommended and recorded a similar operation. This operation consists in scrubbing the adjacent surface of the liver and diaphragm with sponges, stitching the omentum to the anterior abdominal wall, and draining the pouch of Douglas by means of a glass tube. Schiassi afterwards advised that the omentum should be sewn into the wound.

Dr. Bernget† has collected the records of 288 cases, and shows that, in spite of the operation being not yet out of its experimental stage, in about 30 per cent. of ascitic cases the ascites has been cured.

The figures collected by Dr. Rolleston‡ seem to indicate that the results of operation are better in the cases of hypertrophic cirrhosis than of atrophic. He says that out of "thirteen cases of hypertrophic cirrhosis tabulated by Guillot, ten were cured: Greenough adds four cases, making up a total of seventeen cases, of which thirteen were relieved," whereas in atrophic cirrhosis, out of 104 cases only forty-four were improved, and no more than nine were living and in better health two years afterwards.

The question must now be asked, in what way does the operation affect the cirrhosis? It is usually supposed that it acts by setting up a collateral circulation, but if it be merely a question of blood supply, why should the disease have started, seeing that its arterial supply was then far better than any subsequent operation could make it? The disappearance of cirrhosis after operation reminds us of the occasional disappearance of cancer after unsuccessful attempts at removal. Parenchymatous goitres are also apt to disappear when parts of them are taken away, and, what is still more to the purpose, Bright's disease is also occasionally cleared up by stripping the kidney of its capsule. It is to be noted that in each of these different diseases cure does not inevitably follow the operation even when the circumstances seem to be similar. On the contrary brilliant results may ensue in a seemingly advanced and unfavourable case, and there may be complete failure in one much less severe. Though the chances of success seem to be better in the case of goitre than of cirrhosis of the liver, and better in cirrhosis

* 'Berlin. klin. Wochenschr.,' 1893, Bd. xxxv, S. 833.

† 'Die Talma-Drummondsche Operation,' Jena, 1905.

‡ 'Diseases of the Liver,' pp. 260 and 326.

than in Bright's disease, and least of all in cancer, yet all are more or less capricious in their response to operation. It is highly probable that whatever explanation is applicable to one of these instances is applicable to all. Just at present no explanation seems quite satisfactory, but the fact that they all behave after the same fashion as the result of operation helps to link them together in their pathology.

We have ourselves performed the operation three times. One patient did well until the seventh day, and then died suddenly in the night from angina pectoris.

In the second, a case of hypertrophic cirrhosis with intense jaundice, which was sent to us by Dr. Murrell, the result was eminently satisfactory. In this case the skin was so yellow and the bile so completely absent from the fæces that the presence of a calculus or of cancer was suspected. The gall-bladder was therefore opened, and the absence of obstruction proved by the easy passage of a probe along the cystic and common ducts into the duodenum. A piece of liver was cut off for examination, the adjacent peritoneal surfaces of the liver and diaphragm were well rubbed with a sponge, and the omentum was tied to the margins of the wound.

The following points in this case are worthy of note.

The jaundice and other symptoms had not been persistent since they set in, but had at one time undergone remarkable diminution. So also after the operation they at first cleared off, then there was a slight relapse, and after that another and slighter before the last trace of jaundice went away.

The results of the operation were very striking, and exceeded all expectation. The patient had been sick two or three times a day for weeks before, and had been exceedingly weak and depressed. These symptoms, as well as the intensity of the jaundice, led us to take a very grave view of the operation. Indeed, according to Monro and McGregor,* "the occurrence of jaundice in the disease is generally held to bar surgical intervention."

Before the patient became jaundiced her hair was black. When we saw her it was white, and the contrast between the brilliant yellow skin and the thick crop of snow-white hair was very remarkable. After the operation the hair rapidly became black again.

The lower margin of the liver, which at the time of the operation had reached about the level of the navel, within six weeks afterwards had receded to its proper level.

When examined under the microscope the liver showed changes

* "Epipoplexy for Cirrhosis of the Liver," 'Lancet,' 1906, vol. i, p. 1240.

characteristic of biliary cirrhosis with extensive degeneration of liver-cells, very few of which could be termed normal. It seemed almost impossible that such widespread destruction could ever be remedied, but Max Borst* says that von Meister has removed so much as four-fifths of the liver from rabbits, cats, and dogs and that the whole of it has been replaced with new tissue in from forty-five to sixty days.

In the third case the cirrhosis occurred in a soldier, aged 35 years, a patient of Dr. Hope's, and was apparently of syphilitic origin. There was both jaundice and ascites. The liver was moderately enlarged, and a microscopic section showed changes indicative of a mixed form of cirrhosis, the bands of fibrous tissue enclosing in some parts lobules and in others groups of lobules. Recovery was slow but sure. A small quantity of ascitic fluid re-collected, but was not tapped, and eventually disappeared. In this case, too, the general rejuvenation after the operation was pretty conspicuous, but was not nearly so pronounced as in the former case.

Acute Yellow Atrophy.

Acute yellow atrophy is usually held to be bacterial in origin, although it is noteworthy that no special bacterium has ever been isolated. The cardinal signs of inflammation (that is, the reaction of the organism to injury) may, moreover, be absent, so that there is neither *rubor*, *tumor*, *calor*, nor *dolor*. In very acute cases intoxication may possibly be too virulent for such signs of reaction to show themselves, but this can hardly be said of those which run a course extending over some weeks, and in these also there may be no signs of inflammation. Some of the reasons for thinking that this disease and cirrhosis are but different varieties of the same disease† are as follows, namely :

(1) Like some of the degenerations of organs, acute yellow atrophy is markedly influenced by pregnancy. A condition which may be regarded as part of the way to acute yellow atrophy occurs, according to Miotti,‡ in the liver of normal pregnancy. He found on examining the livers of guinea-pigs at various stages of gestation, that here and there the hepatic cells are enlarged and contain granules or droplets of fat arranged round the nuclei. Near the

* 'Die Lehre von den Geschwülsten,' Bd. i, S. 558.

† E.g. Dr. Findlay, 'Brit. Med. Journ.,' 1900, vol. i, p. 1330; also Obrzut, 'Medizin. Jahrbücher,' Wien, 1886, S. 463.

‡ 'Annali di Obstetricia e Ginecologia,' vol. xxii, 1900, p. 733.

full term of gestation this intra-cellular fat is much increased, and Miotti regards it as a degeneration product and not a mere infiltration.

This seems to be the physiological pretext for the disease, such an antecedent, in fact, as we notice in other diseases of development and of growth. It reminds one of the natural fulness of the thyroid gland of women at puberty, which accounts for their susceptibility to goitre, of the increase of red marrow, usual in pregnancy, which is the precursor of osteomalacia and of other similar physiological antecedents of pathological events.

We ourselves have seen an instance which seemed to be on the borderland between the physiological and pathological.

This occurred in a previously healthy married lady, aged 30 years, who was carrying her fourth child. When four months had passed by she became slightly yellow and indefinitely out of health. Then vomiting set in, and the mouth and lips became dry. The urine was now opaque, scanty, of a reddish yellow colour, and on evaporation abundance of tyrosin was found, but no leucin. The temperature was raised from one to two degrees. She was weak, apathetic, and delirious at night. The motions were normal, and there was no tenderness over the liver area, though the usual dulness had receded by about 2 cm. Dr. Hurry, who saw her with us, agreed that her condition was suggestive of incipient acute yellow atrophy, though he hesitated to say that the disease was actually present. The patient was decidedly ill for nearly three weeks, and then gradually became better, but remained jaundiced and in indifferent health until she had passed through her "confinement."

Sometimes *icterus gravis* first appears during the *puerperium*, though it seems probable that in some, if not all, of the cases the liver was in reality diseased before child-birth. Colm* describes a case which was precipitated by an attack of puerperal septicæmia. This set in on the fifth day; forty-one days afterwards definite *icterus gravis* appeared, after a period of preliminary jaundice, and proved fatal.

Of 22 cases collected by Frerichs one half occurred during child-bearing, and this proportion is in keeping with the figures collected by Legg and by Thierfelder.† Legg found that 25 out of 69, and Thierfelder 33 out of 88 in women were associated with pregnancy.

(2) Just those circumstances which are known to facilitate or to precipitate the degenerations are often accountable for acute yellow

* 'Zentralblatt f. Gynäkol.,' 1904, Bd. xviii, No. 34, S. 1009.

† 'Quoted by Osler, 'Text-book of Medicine,' p. 459.

atrophy, and when they do so they are usually present in an intensified degree.

In addition to pregnancy, *alcohol, syphilis, septicæmia, influenza,* and other *bacterial intoxications,* and *depressing circumstances* in general, are probably by far the most important of the producers of chronic presenile degeneration of organs; and the same factors acting in concentrated form are responsible for most cases of icterus gravis. A prolonged alcoholic debauch, syphilis associated with pregnancy, illegitimate pregnancy and its accompaniments of dread, shock, grief, and mental depression are among the chief precursors of acute yellow atrophy.

(3) Acute yellow atrophy is also, like the degenerations, influenced by age, locality, and sex. It occurs as a rule between twenty and thirty, in the female, and is more uncommon in some districts or countries than others. It is apparently unusually rare in America, for Professor Osler says he has never seen a case.

(4) Both *structurally* and *clinically* cirrhosis and acute yellow atrophy may be identical in all essential particulars. A cirrhotic liver is an atrophied liver plus the increase in its fibrous tissue; and the liver of acute yellow atrophy is also cirrhotic. The so-called new bile-ducts are features common to both. It is true that in the one disease the most striking change is of the fibrous tissue, and in the other of the secretory cells, but between these two are all manner of gradations.

As it is with the structural changes so is it with the functional, for if we leave out mere mechanical effects the symptoms of the two diseases are also fundamentally alike. The symptoms of acute yellow atrophy are those of an acute form of cirrhosis, and the final symptoms of cirrhosis are those of chronic atrophy. A good instance of this is shown in the report of a case of Dr. Tidey's,* in which there were cerebral and other symptoms characteristic of acute yellow atrophy, and lencin and tyrosin were present in the urine. Yet after death the liver showed only the appearances typical of atrophic cirrhosis.†

There is sometimes great difficulty in deciding whether a given illness is due to the one disease or to the other. Among these debatable cases is one of special interest recorded by Dr. Carrington.‡

* 'Brit. Med. Journ.,' 1892, vol. ii, p. 125.

† See also among others, "A Case of Acute Biliary Cirrhosis, clinically simulating Acute Yellow Atrophy of the Liver, Fatal in Twenty-four Hours," by Dr. R. Shingleton, 'Brit. Med. Journ.'

‡ "Acute Atrophy or Acute Cirrhosis of the Liver," by Dr. Carrington, 'Trans. Path. Soc.,' 1885, vol. xxxvi, p. 218.

The patient, who was a heavy beer drinker, died after an illness lasting four days, in which delirium and eclampsia were predominant symptoms. At the autopsy there was found to be considerable increase in the connective tissue round the portal canals. The case was brought before the Pathological Society of London, and a piece of the liver submitted to a committee, which reported that the liver "appears to be identical with a case of cirrhosis and acute yellow atrophy of Dr. Cayley's.*

Other instances are recorded in which acute yellow atrophy apparently supervened on cirrhosis. Dr. Ven,† of the Victoria Hospital for Children, published an account of a patient with acute yellow atrophy preceded for so long as eight months by all the symptoms of hypertrophic cirrhosis.‡ Such cases apparently correspond with those in which acute Bright's disease supervenes on the chronic form, and their pathology is no doubt the same.

Of course, it is possible that in acute yellow atrophy, and also in cirrhosis ending in a similar manner, there is not only degeneration, but intoxication as well. If we look upon both the diseases as primary presenile degenerations in the first place, we know that all organs so affected have lost some of their ability to resist the attacks of micro-organisms. It is not improbable that some microbe or the toxin of some organism which has its home in the intestines, may gain a footing in the weakened organ and hasten its downfall. But as a matter of fact, notwithstanding the most careful investigation, no poisonous micro-organism has yet been detected.

On the whole the evidence obtainable seems to point to the conclusion that acute yellow atrophy of the liver is a true presenile degeneration of highly malignant type, that it may be either spontaneous in its origin or be set going by some toxin, such as that of syphilis, of yeast, or of influenza or other disease bacteria. It in all probability, as a rule, if not invariably, supervenes upon a previous defective development.

The *tout ensemble* of the disease is in accordance with this view. Its occurrence at an early age is just what we should expect of a cirrhosis of this consecutive kind. Moreover, it corresponds with other consecutive degenerations in its virulence and in the fact

* 'Trans. Path. Soc., London,' vol. xl, 1890, p. 137.

† 'Lancet,' August, 1884, vol. ii, p. 191.

‡ Also extreme "Hepatic Cirrhosis of Childhood; Typhoid Fever; Death from Acute Yellow Atrophy in a Child of Six," by Mr. C. M. Powell, 'Brit. Med. Journ.,' 1897, vol. ii, p. 1086; also "Cases in Young Children," by Dr. Ormerod and by Dr. Cayley, 'Trans. Path. Soc. London,' vol. xxxiv, 1883, p. 127.

that it is sometimes hereditary. "Graves has recorded the remarkable case of two sisters who died of this disease in succession at an interval of eight months, while three months later a third sister was attacked with a jaundice which threatened to take the same course, but from which she recovered."* Dr. Fagge,† from whom this quotation was taken, further on refers to some cases published in 1834 by Dr. Griffin, of Limerick, which bear evidence of being of a similar nature, and are so recorded: "Four children of the same parents were attacked within a few weeks by jaundice with cerebral symptoms. Two of them died, but two recovered after having been in a state of almost complete coma."

The Association of the Cirrheses with Similar Degenerations of Other Organs.

In accordance with the rule that the primary diseases of development are most often coincident in organs most nearly related in structure and function, we should expect that the organs usually affected simultaneously with the liver would be the circulatory and the renal, and this view is apparently correct. Dr. Price‡ found that there was *chronic Bright's disease* in 18 per cent. of the 142 examples of cirrhosis collected by him. In 78 cases from the Massachusetts Hospital by Drs. Sears and Lord,§ 23, or 29.5 per cent., were found to have chronic Bright's disease.

The latter writers found that general *arterial sclerosis* was present in an even greater proportion, for it occurred in 49 cases, or 60 per cent. Hence it would appear that the arteries are in reality more often the seat of fibrous degeneration in cirrhosis than the kidneys.

After the arterial system and the kidneys the solid organ most closely associated with the liver in a natural way is probably the *spleen*, and this seems to come next in order in the frequency with which it is affected with senilism. The spleen is said often to show degenerative changes in Bright's disease. It is usually bigger than normal, is often fibrous, and its capsule shows a certain amount of inflammatory thickening or is adherent to adjacent organs. Allusion has already been made to some of these cases of combined liver and spleen disease. We shall also come across them in the chapter on disease of the blood-making organs, for they serve as a connecting

* 'Clinical Medicine,' p. 459.

† 'Fagge's Medicine,' ed. 1, vol. ii, p. 267.

‡ 'Guy's Hosp. Reports,' vol. xlii, 1884, p. 295.

§ 'Boston Medical and Surgical Journal,' vol. cxlvii, 1902, p. 285.

link between the developmental diseases of these two sets of organs. Instances are occasionally recorded of the three—liver, kidneys, and spleen—being affected together. The association may be even still more widely distributed, as, for instance, in a case recorded by Dr. Freeman, of New York,* in which a boy, aged 10 years, had a large fibrous liver, perisplenitis, parenchymatous nephritis, indurated pancreas, and polypoid growths in the colon.

In regard to this induration of the *pancreas*, Amato† has arrived at the conclusion, as the result of his investigations, that it is frequently affected with fibrosis when there is cirrhosis of the liver. He examined six cases of the latter disease minutely, and found increase of the peri-lobular connective tissue of the pancreas in all, though it varied greatly in degree.

This opinion is borne out by Lefas,‡ who investigated the state of the pancreas in many cases of cirrhosis of the liver, and found sclerosis in a large proportion. He says that the changes are found in both atrophic and hypertrophic cirrhosis, and closely resemble whichever disease is present, so that if the liver be enlarged so also is the pancreas, and *vice versa*. In those unusual cases in which many organs are simultaneously affected with fibrous degeneration, the explanation has been advanced that the association is due to a “fibrous diathesis.” But such a statement is in reality no explanation at all, for it does not carry us any farther. It is only putting into other words the self-evident fact that such fibrous degenerations are the outcome of some mysterious proclivity to degenerate which is possessed by some people to a far higher degree than by others.

One of the most interesting of associations is that of cirrhosis with *pre-natal absence or blocking of the common bile-ducts*. It is usually believed that in this disease the cirrhosis is produced by the blockage of the ducts, but there is good reason for supposing that this interpretation is not correct, and that the two conditions have little, if any, causal connection. Thus it is noteworthy that in this form of cirrhosis there is, as a rule, a very great development of fibrous tissue. This being the case, it seems curious that in obstructive jaundice in adults the new fibrous tissue, if there be any at all, is, as a rule, very scanty.

Further, it has been observed that if the bile-ducts of an animal be tied, and the parts kept aseptic, little or no fibrosis results, but

* ‘Proceedings of the New York Path. Soc.,’ 1897–8.

† ‘Riforma Medica,’ September 16th, 1903, vol. xvix, p. 1013.

‡ ‘Arch. générales de Méd.,’ 1900, N.S. iii, vol. 1, p. 539.

merely focal necrosis of liver cells,* and a similar result occurs in human beings when the bile-ducts are occluded by the presence of a malignant tumour. Moreover, Neumeyer, in his work on gall-stones, declares that obstruction from biliary calculi does not give rise to cirrhosis. Besides, the observations of Parker,† of Bristol, go to show that the cirrhosis is a variable one, affecting different parts to a varying degree in different cases, and that there is reason to believe that the morbid process is rather descending than ascending. Again, he shows that the symptoms produced and the character of the cirrhosis found after death may not tally with the symptoms and character of the condition which is known to result from obstruction of the bile-ducts by the presence of calculi, and concludes that "on the whole, then, we have in some of these cases at least a complete picture of hypertrophic biliary cirrhosis, only different from that seen in adults by the results of secondary obliteration of the bile-ducts." It is also to be noted that the cirrhosis which results from the experimental production of hepatic cirrhosis‡ in the lower animals is not hypertrophic, but is an interlobular form, in which the hepatic lobules atrophy from without inwards.

Hale White§ dwells on the rarity of obstructive cirrhosis. He says that in the course of a considerable *post-mortem* experience he has only twice seen obstruction associated with cirrhosis, and alludes to the investigation of Ford, who searched through the Surgeon-General's Library at Washington from the records of 1882 to 1900, and could only find twenty-one cases. To these Ford adds those which he has seen himself. Of these twenty-one cases thirteen were in adults, and it is possible that in some of them alcoholic drink was the cause, and not the obstruction of the duct. All the rest, eleven in number, were instances of pre-natal obstruction of the duct. It seems very improbable that obstruction of the duct should rarely, or never, give rise to cirrhosis when it occurs in the adult, and should nearly always do so, and to an extreme degree, when it takes place in the infant. Hence we see that the evidence is decidedly against the view that the cirrhosis is solely or even largely due to obstruction. It seems more likely that the obstruction and the cirrhosis are related to one another chiefly because they are

* Dr. Rolleston, 'Encyclop. Medica,' vol. vi, p. 502.

† 'Lancet,' 1901, vol. ii, p. 520.

‡ Dr. Vaughan Harley and Dr. Wakelin Barratt, 'Journ. Path. and Bacteriol.,' vol. vii, No. 2, 1901, p. 203.

§ 'Brit. Med. Journ.,' 1903, vol. i, p. 533.

primary disorders of development occurring in naturally associated parts. The disorder is in all probability one of defective development in the first place leading to premature degeneration in the second.

Cirrhosis may be only *partial*, affecting one portion of the liver and not the remainder, as in a case of Dr. Hale White's,* in which, of a liver constricted by a band, one half was cirrhotic and the other half fatty. This patient had also *large white kidneys*. It was not known whether the band was pre-natal, the result of acquired disease, or of tight lacing.

Another partial case is given by Dr. Hall.† It occurred in a girl of eleven, was not due to alcohol, and was associated with *leucocythæmia* and enlargement of the lymph-glands of the mesentery, groin, and axilla. In the liver the left lobe was much atrophied and hobnailed, but "the right lobe showed a smooth, normal surface and thin edge," with the exception of a single nodule of cirrhosis similar to that on the left.

We ourselves have seen a good instance of cirrhosis of the liver complicated with marked enlargement and *fibrosis of the spleen*, in a girl whose brother was at the time undergoing treatment for *progressive muscular dystrophy*. These patients were under the care of Dr. Francis Hawkins, to whom we are indebted for permission to see them. A *post-mortem* examination was made of the first case. It was in all probability one of Banti's disease.

Diabetes and cirrhosis of the liver may occur together, though there is no evidence whatever that the one is the cause of the other. Professor Palmer‡ and Dr. Triboulet§ have especially called attention to the conjunction of these diseases.

Anatomy and Pathology.

ATROPHIC OR PORTAL CIRRHOSIS.

The most remarkable feature of atrophic cirrhosis is the hyperplasia of fibrous tissue. So noticeable is this hyperplasia that it alone was at one time believed to constitute the disease. It was thought that the new growth of fibrous tissue so encroached upon and compressed the liver-cells as to cause their wasting, and that

* 'Trans. Path. Soc., London,' 1886, vol. xxxvi, p. 263.

† 'St. Bartholomew's Hosp. Rep.,' vol. xxviii, 1892, p. 1673.

‡ 'Berlin klin. Wochenschr.,' Bd. xxx, 1893, S. 815.

§ Triboulet, 'Gaz. Hébd. de Méd. et de Chir.,' N.S. Tome i, 1896, p. 376.

this was the sole explanation of the atrophy of the secreting cells, and of all the phenomena which proceeded from it. But this view is now regarded with scepticism. It is now usually held that the morbid process begins in the liver-cells, the fibrous tissue being of secondary formation.

Though it is no doubt true that the disease occurs primarily in the liver-cells, yet it is highly probable that there is a process of contraction going on in the new fibrous tissue, and that this contraction is capable of reducing a liver which is too big to one which is too little. Its reality is evidenced by the well-known fact that the lobules of a cirrhotic liver stand out on section, suggesting that they had previously been in a state of compression. Moreover, in some cases of nodular cirrhosis the hepatic cells at the margin of the nodule seem to show the effects of pressure by becoming spindle-shaped. On the other hand, Dr. Payne* and Professor Lionel Beale have pointed out that the atrophy of the liver-cells may be seen at the beginning of the disease and cannot therefore be the result of compression. They believe that the excess of fibrous tissue is secondary, and occurs as the result of an attempt to fill up the gap created by the atrophy.

A process seems to be in action similar to that which takes place when the brain atrophies in old age. Sir G. M. Humphry showed that under these circumstances the negative pressure within the skull may lead to a deposit of new connective tissue, in the form of bone, on the inner aspect of the skull cap.

The two cases are, however, hardly analogous, for in the one we have to deal with a rigid box, in the other with a highly elastic, or, at any rate, flexible capsule. Moreover, we often see similar proliferation of fibrous tissue taking place not only during contraction, but even in the very act of expansion. Sections cut from some livers with hypertrophic cirrhosis still undergoing increase in size show that new fibrous tissue is being laid down all the time. Further, it has been pointed out that the projections on the surface of hobnailed livers are often due, not so much to contraction of the fibrous tissue, as to the proliferation of liver-cells or adenomatosis.

Although each of the two chief forms of cirrhosis has its own clinical and structural characters, it is now known that those characters which used to be thought distinctive of the one form may also be observed in different examples of the other. In reality it is only the combined features of each which are distinctive, the

* "Address to the Pathological Society of London," 'Brit. Med. Journ.,' 1888, vol. ii, p. 1327.

details are not. Hence we shall not go wrong if we now restrict our discussion to one form only, and the better of the two for our purpose is hypertrophic cirrhosis.

Hypertrophic or Biliary Cirrhosis.

One of the chief features of some microscopical sections of cirrhosis is the multiplication of liver-cells, shown by their manner of staining, their large size, and the occurrence of karyokinesis or of actual nuclear division.

This proliferation of secretory cells may be explained in one of three possible ways:

(1) It may be the expression of an attempt at compensation or repair (Hanot).

(2) The whole of the morbid process may be regarded as a sort of adenomatosis (Max Borst).

(3) The new fibrous tissue, the proliferated liver-cells, the new bile-ducts, and the molecular degeneration may all be manifestations of presenile degeneration.

It is noticeable that at the outskirts of a lobule of a cirrhotic liver the liver-cells are undergoing a process of simplification, brought about by granular or fatty change of their cytoplasm, followed by denudation or absorption. This absorption is probably the work of the fibroblasts, endothelial derivatives and lymphocytes, though it is seldom that they can be actually detected in contact with the secretory cells. Nevertheless, the denuded and more or less rounded cells derived from liver elements can be seen mixed up with these phagocytic cells.

At this point we come to debatable ground, for there is a similar difference of opinion in regard to the destination of the simplified liver-cells as there is in regard to the destination of the epiblastic cells which surround skin cancers. Some (*cf.* Hamilton,* Kelsch, Wannebroneq) believe that the liver-cells ultimately become transformed into fibrous tissue. Others say that it is not possible for cells derived from the hypoblast to change into a mesoblastic structure.

Thus Dr. John McIntyre, in his John Reid prize essay on "Some Points in the Formation of the Connective Tissue of the Liver, with Special Reference to Hepatic Cirrhosis,"† the outcome of a close study of this subject, comes to the conclusion that no such transformation of liver-cells into connective tissue takes place.

* 'Text-book of Pathology,' 1894, vol. ii, pt. i, p. 219, fig. 306.

† 'Glasgow Med. Journ.' 1901, vol. iv, p. 341 and 415.

Though the liver-cell may not itself undergo a change into connective tissue, yet it is by no means impossible that it may, in the course of its retrogression, at last arrive at a stage when it is no longer an epithelial structure. What then undergoes transformation is not a liver-cell, but a cell so elementary that it belongs to a stage preceding the division into the three germinal layers. In fact, we do actually see the liver-cell in process of reversing its development until it assumes the round-cell pattern, and it is not

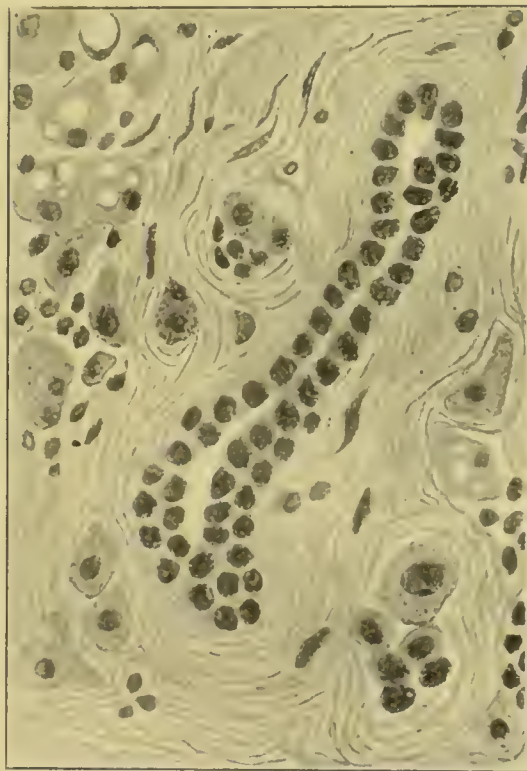


FIG. 4.—The organ is in process of reduction to a simpler state. The liver cells are either undergoing peripheral absorption or are proliferating. Running diagonally athwart the section are rows of partly denuded cells arranged in tubular form. Many cells of low type are becoming transformed into new fibrous tissue.

unlikely that it continues to do so until it arrives at the equivalent of the morula stage of development. It is now at the limit of its degradation as a constituent of an organ, and there seems nothing inherently improbable in believing that at last it becomes so simplified by denudation or proliferation as to finish its career by becoming a constituent of fibrous tissue.

It is held by some authorities that the new fibrous tissue is derived neither from liver-cells nor from the transformation of phagocytes of endothelial or lymphocytic origin, but comes solely from the proliferation of connective-tissue cells. The whole ques-

tion is still unsettled. There is undoubted multiplication of these cells. They probably act as phagocytes, and, having increased in number and done their work, the mere return to their resting state would account for the excess of fibrous tissue, without having to call in the aid of a replacement hypothesis.

Whichever view is correct it is possible to trace in sections of cirrhotic livers all gradations between perfect polygonal liver-cells, through the intermediate stage of columnar cells, to rounded cells of the simplest possible type. Moreover, in the same way that the single liver-cell which has reverted to the protozoan pattern (or cancer-cell) cannot remain idle, but goes through the treadmill task of unceasing and useless proliferation, so also when the cells which together make up the liver as an organ revert to their elemental metazoan pattern, analogy would seem to indicate that they, too, most likely spend their time unprofitably in the continuous manufacture of unnecessary fibrous tissue.

In the course of this reduction or reversal of development the formation of the new bile-ducts may be regarded as a half-way stage, because they come mid-way between the highly organised liver-cell and the simple round cell of lymphocytic or fibroblastic type.

The whole process of cirrhosis is, in short, one of reduction of the liver from a highly developed organ to one of embryonic simplicity. As a matter of fact it never reaches to this extreme, but continues until function is so far reduced as to be incompatible with life.

This view is consistent with that held by Adami, who believes that the appearance of new bile-ducts is due to a reversion to the original form of hepatic follicles, such as are found in the earliest stages of the development of the liver. He suggested for it the name of "reversionary degeneration."*

As a fact the embryonic liver is a tubular organ derived from the hypoblast. Into this mass of tubes the new ducts push their way from the (hypoblastic) primitive gut.†

To sum up, all that is known about atrophic and hypertrophic cirrhosis tends to the conclusion that they are but two varieties of the same disease. The "hypertrophic" form corresponds with the giant hand, with scleroderma, with the large white kidney, and with pseudo-hypertrophy of muscle or of brain. Compared with the atrophic form it is a disease of early life, is usually, if not invariably, idiopathic, is sometimes hereditary, and is characterised by over-

* 'Green's Pathology,' p. 487. See also Max Borst, 'Die Lehre von den Geschwulsten,' Bd. ii, S. 538.

† 'Shore and Jones, 'Journ. of Physiology,' vol. x, 1889, p. 408.

growth and degeneration. It is, in short, a degeneration, and, like degenerative hyperplasia of some other organs (*e. g.* muscle), it may, possibly, in course of time, shrink into the atrophic form.

Atrophic cirrhosis, on the one hand, is a pure senilism, for it is distinguished by wasting rather than growth, occurs late in life, and corresponds with the granular contracted kidney, with cortical degeneration of the brain, with tabes of the spinal cord, and with other fibrous contracting senile processes.

Cirrhosis as a Variation.

Hypertrophic cirrhosis, when it occurs in its most characteristic form, answers to the description of a regressive variation of major degree, for it has no extrinsic cause, is a disease of early life, is occasionally accompanied by other spontaneous degenerations (*e. g.* splenomegaly), is sometimes hereditary, and has all the aspects of being a quasi-physiological or para-physiological condition. It is, in short, a discontinuous variation or mutation.

So also typical **atrophic cirrhosis** is a continuous variation or fluctuation, for though it has its origin in some spontaneous para-physiological change, it is fostered or produced by the definite cell environment of alcohol. But though largely of intrinsic or inborn origin it is not hereditary. It is the expression of an inherent tendency to variation, and is not the outcome of the inheritance of a specific variation.

Summary ; Conclusions.

When we take a comprehensive view of a liver affected with ordinary atrophic or portal cirrhosis we see that the whole organ is undergoing rapid deterioration.

When this deterioration first sets in the liver is a structure of high organisation. Every part is of the best possible kind. Its cells are so shaped as to fit together into orderly groups, each group being so disposed in relation to other groups that every projection and every recess is utilised to the full, and the organ, as a whole, carries out its work economically and efficiently and without a trace of friction or fatigue.

After the blight of cirrhosis has passed over it that which remains is no longer a well-defined organ, but consists rather of heterogeneous collections of cells of all shapes and sizes mingled together into a more or less confused mass. From among this wreckage one

can still pick out cells recognisable as liver-cells, but many are so diminished in size and altered in shape as to be distinguished with difficulty, or not at all. In that part of the liver structure in which degradation is most advanced there is nothing but a disorderly crowd of cells of inferior type intermingled with fibres or elements intermediate between cells and fibres. Next come dense bands of useless fibrous tissue closing round and strangling deformed lobules or adenomatous collections, and seriously adding to the difficulties of the already embarrassed organ. Taken out of the body the liver ceases to present the shapely appearance of the healthy organ, with its clean, smooth, glistening surfaces, sharply-cut edge, and contours exactly moulded to those of adjacent organs. On the contrary it lies on the *post-mortem* slab a stiff, ill-shapen mass, rough and corrugated, and of leathery hardness.

It is patent to anyone who examines such a liver that its functions must suffer to a degree which corresponds with the extent of the damage, until, like a machine eaten away with rust, it can go on no longer, and, after more and more obvious complaint and disease, comes at last to a standstill.

Obviously the process has not reached its limits. We only see things at a halfway stage. Were it possible for it to continue to finality what would be left would evidently be no more than the rudiments of an organ—an amorphous mass of round-cells and fibres with but a trace of organisation and capable of performing only the simplest functions.

It is scarcely less obvious that the result of this depreciation of an important organ in an otherwise sound body is to bring it back as nearly as may be to the position from which it started. In the beginning the liver consists of an incoherent mass of cells of great simplicity of form and function. These, by development, become more or less square and arrange themselves into a tubular organ. Ultimately, by continued refinement, the cells increase in size and attain a shape which is pentagonal or hexagonal on section, grouping round systems of blood-vessels and ducts, much as the bricks of a well-built house are grouped into rooms round the pipes and the apertures for the supply of air, water and gas, and the vents for smoke and sewage. The cirrhotic process consists in the breaking down of the details of the liver structure in order to reduce it to its original elements, as when a house is demolished until ultimately nothing is left but a heap of builders' material, as at the beginning.

The agents in this work of simplification are the phagocytes. These gather about the decaying cells, not for the purpose of des-

truction, but of sanitation. When they appear the process of cell-degradation has already set in. Granular, or fatty, or other less notable changes have begun on the outskirts of the cells, and the phagocytes do no more than remove this useless material. These phagocytes are derived partly from the blood, partly from the setting free of reversed connective-tissue corpuscles (fibroblasts) from the stroma, and partly from similar reversion of endothelial cells.

They swarm on the outskirts of the lobules, busily absorbing the effete cytoplasm, and in part constitute the so-called inflammatory cells of the older histologists. Among these are also the rounded cells, almost bare of cytoplasm, reduced from the original liver-cells.

During the whole of this levelling process the cells retain their function, though undergoing progressive debasement, for they are by no means passive, but at each stage of regression perform the work they had previously accomplished at the corresponding stage of their progression. Hence, when they have been reduced to a shape suitable for a tubular organ they multiply and rank themselves into the semblance of a tube. But even in the process of doing so the work of degradation and denudation still goes on, so that the tube-form is soon broken up by the further degeneration of some of its elements into more rounded cells. These still further proliferate, and having arrived at a connective-tissue stage of regression, they possibly elongate, first into spindles, and then into the constituents of fibrous tissue.

One important feature of this devolution must be emphasised, and that is the proliferation. The liver-cells apparently increase in their rate of multiplication from the first onset of degradation until they reach their resting-place, and become imbedded in layers of inert fibrous tissue.

The question may now be asked, Why does the work of degeneration stop at the connective-tissue stage of cell development? Why does it not go back still further to the starting-point, prior to the formation of connective tissue? The answer, of course, is that the liver, as an organ, can only degenerate until it reaches the stage which corresponds phylogenetically with the beginning of the primitive organisms. It has then arrived at the limits of its evolution as a collective cell organisation. It is quite possible that one, or some, of its cells may break through these social restraints, acquired by long ages of custom, so that they degenerate, beyond the organ, into the single cell or protozoon era.

When this ultimate degeneration takes place the cells throw off all restraints of multiplication, such as have been imposed in order to render them fit for existence within the confines of an organ, and proliferate wildly as a cancer. More often the effect of the degeneration of single cells is expressed, not by cancer formation, but by the less violent debasement which gives rise to overgrowth. In other words, the degenerating liver, like the degenerating thyroid, is often the seat of adenomatosis.

We must next insist that this retrograde process is indistinguishable, except in degree, from the retrograde changes of normal old age. Normal senile degeneration is seldom, if ever, distributed over all parts of the body alike. Almost invariably it is decidedly partial, so that many organs may remain unaffected, even when a period is put to existence in a perfectly natural manner. Hence many people die from old age without showing a trace of degeneration in their livers. At the same time it is quite common to find that the liver of the old man presents all the characters of early cirrhosis without discernible cause and without revealing itself by any symptom.

Furthermore, the cirrhotic process exactly tallies with that characteristic of senile decay. This, too, essentially consists in a reversal of ascending development—a return to a state of affairs comparable with that which exists in the tissues of the embryo.

Ordinary cirrhosis is, in short, a senile decay highly exaggerated, as befits an organ undergoing degeneration while the rest of the body is still young.

This premature senility is brought about by the operation of two agencies. The first is reversal. The organ, working steadily and easily, begins to swing back in its development and continues to do so, with occasional interruptions or exacerbations, until it is reduced almost to its primitive simplicity. It would take too long to explain here why this retrogression takes place. That has already fully been explained in the chapter on variation and rhythm (see p. 103).

It is enough that we should say here that the liver has been reminded of a time in its evolution when its existence was far shorter than it is now. The reminder is furnished by the persistent use of alcohol or of some other toxin. This toxin, flowing among the liver-cells day after day for, perhaps, months or years together, acts as a pernicious environment tending to degrade them to their primeval state. Ordinarily, no such retrograde change takes place, no matter how much alcohol is brought into contact with the cells. What is essential is that this morbid environment should act in con-

junction with a wave of depression started at some early stage of the liver's existence. The two—the decadent tendency and the environment—working together, cause the downfall of the organ by a process of backsliding. Exactly the same process goes on, in effect, as in an act of memory. An event occurring in the early life of a man is said to be forgotten. As a matter of fact the vibrations which were then set going in certain brain-cells were not abolished, but were merely covered up by subsequent events. The rhythm, once established, continues in a latent form, and so it remains, unless a corresponding or allied event starts a vibration of similar nature. The original vibration is then so magnified as to affect consciousness and revive memory.

Alcohol is a toxin with properties of a debasing nature which may happen to re-awaken a long forgotten impulse of similar kind. The reminder, alcohol, awakens memory, not in the brain, but in the liver-cells, causing them once more to become old—to enter upon their second childhood—at an age at one time normal, but now premature. In short, there is a return to a previous state, and so cirrhosis (portal) springs into being. In such a case we have all the constituents of a *minor or continuous variation*.

A *major or discontinuous variation* occurs when a wave, started in remote evolutionary time, and rendered latent, is suddenly exaggerated, and so revealed: not by any contemporary event, such as alcohol, but by the union of two or more similar impulses. The two rhythms, coinciding, double their original volume and so again bring about the senile condition which we term “cirrhosis.”

Such a combination is effected by marriage when both husband and wife possess latent tendencies to liver reversion. The cirrhosis originated in this way is, of course, the spontaneous variety, usually or invariably biliary.

The Relation of Cirrhosis to Cancer Formation.

Carcinoma.—Max Borst,* says that it is possible for cirrhosis to present itself in the form of generalised cancer. This “cirrhosis carcinomatosa” reminds us in some respects of certain alveolar cancers of the rectum, for there are large alveoli, and usually no metastases. Hence, though malignant, it is only locally malignant.† This malignant, or semi-malignant, degeneration of the liver does

* ‘Die Lehre von den Geschwülsten,’ Bd. ii, S. 558.

† Described by Rénon, Géraudel, and Monier-Vinard (‘Arch. de méd. Expér. et d’anat. path.’ Tome xxii, 1910, p. 311), under the new name of hepatoma.

not proceed centrifugally from one point, but begins in several different foci, and does not give rise to the usual clinical symptoms of malignancy. Max Borst evidently inclines to the view that it precedes the cirrhosis in order of sequence, but doubts whether it can be regarded as a true carcinomatosis. Cases bearing the same interpretation have been recorded by Dr. Pennato,* who mentions many instances of cirrhosis combined with cancer, and says that one lobe of the liver may be enlarged and affected with cirrhosis and carcinoma, while the other is merely atrophied and cirrhotic.† Dr. Rolleston‡ has also described a "cirrhosis maligna" or "cirrhosis carcinomatosis," though in the instance given by him the malignancy does not seem to have been so widespread as in the other cases to which we have referred. It appears to have begun in one part of the liver and invaded other parts in nodular masses. The cells of the cancer took the shape of twisting tubules, and Dr. Rolleston regarded it as due to a misdirection of the new bile-ducts, and, therefore, as secondary to the cirrhosis. He says that Hanot and Gilbert§ have described a case of the same sort under the name of "epithelioma trabéculaire," and that they regard the growth as synchronous with, and due to the same cause as, the cirrhosis. At the same meeting of the Pathological Society at which this paper was read, Dr. William Hunter and Dr. Campbell Thomson showed specimens of the association of carcinoma with cirrhosis. The former expressed the view that the cancer originated from liver-cells by direct transformation, but Dr. Thompson thought that the simultaneous occurrence of the two diseases in his case was a mere coincidence.

Professor Muir,|| in writing on four cases of cirrhosis of the liver with primary cancer, says that the cancer in these cases can in some places be seen arising from the liver-cells, often as multiple foci, and that it is consecutive to the cirrhotic degeneration of liver-cells. A diffuse cancer process once having started would naturally tend to give rise to, or to aggravate, the cirrhosis.

If we suppose that the cancer comes first, then we must regard it as originating in an organ whose tissues are already inclined to undergo widespread degeneration. In that event the cirrhosis is merely the expression in an exaggerated degree of that fibrous

* 'Riforma Medica,' 1897, vol. xiii, No. 105, p. 350.

† See also "Three Cases of Primary Contracting Scirrhus of the Liver Simulating Cirrhosis," 'Trans. Path. Soc., Lond.,' vol. xxviii, 1878, p. 137.

‡ 'Lancet,' 1901, vol. i, p. 180; 'Trans. Path. Soc.,' vol. xxxiii, 1883, p. 172.

§ 'Etudes sur les Maladies du Foie,' 1880, p. 41.

|| 'Glasgow Med. Journ.,' vol. lxvi, 1906, p. 122.

degeneration which usually occurs on the outskirts of all cancers. The degeneration starts in individual cells as a cancerous process, and acts as a stimulus or influence to bring about the downfall of the whole structure.

If, on the other hand, we look upon the cirrhosis as the first in order of time, then it is easy to see that in an organ undergoing degeneration as a whole, a more violent degeneration of certain individual cells may be started into action more readily than is usually the case. The bonds of restraint having already been loosened, and the organ being at a halfway stage, malignancy is but a completion of the process of liberation.

It is already recognised that there is some intimate relation between these processes. Thus Dr. Rolleston,* in writing about the relation between cirrhosis and cancer formation, expresses his opinion that they are both due to the action of a common cause, but believes that this cause is a toxin.

Cirrhosis may also be associated with sarcomatosis, though this is still more uncommon than its association with carcinoma. Dr. W. J. Ford† claims that a case of his, in which a mixed-cell sarcoma existed in a cirrhotic liver, is the first instance to be recorded in which the sarcoma sprang from the new fibrous tissue. Cases are described by Dr. Hale White and by Drs. Finley and Johnston,‡ in which opinion was divided as to whether primary growths in the liver should be termed "carcinomata" or "sarcomata." Probably some of these doubtful cases are instances of endotheliomata.

H. D. Rolleston and R. Salusbury Trevor, in describing a case of "primary sarcoma arising in a cirrhotic liver,"§ give a *resumé* of cases of primary sarcoma of the liver, and say that their case is the seventh on record of the conjunction of cirrhosis with primary sarcoma.

* 'Encyclopedia Medica,' vol. vi, p. 529.

† 'Amer. Journ. Med. Sci.,' vol. cxx, 1900, p. 43.

‡ 'Brit. Med. Journ.,' 1900, vol. i, p. 933; 'Trans. Path. Soc.,' 1885-6, vol. xxxvii, p. 272. The liver weighed 122½ oz. (3472·8 gm.), and was pronounced a carcinoma by a committee of the Pathological Society and a sarcoma by Professors Hamilton and Délépine.

§ 'Journ. Path. and Bact.,' vol. xv, 1911, p. 247.

IV

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF THE KIDNEY

DEFECTIVE DEVELOPMENT OR INFANTILISM OF THE KIDNEY

Important features of infantilism of the kidney are its liability to terminate in early degeneration, and its association with developmental disorders of correlated organs.

INFANTILISM may affect part of a kidney, a single kidney, or both kidneys.

Infantilism of a part of a kidney is a disease of no practical importance except as a "mark of degeneration." It is a sign of unreliability, and is especially indicative of a tendency to degenerate prematurely.

Infantilism of a single kidney, owing to the complete compensation effected by the other, is, as a rule, of very little consequence. But there is reason to believe that under these circumstances the sound organ is more prone to become the seat of calculus, nephritis, or of chronic Bright's disease than when both organs are of normal development. Though pre-natal infantilism of a kidney is a rare event, there are a number of specimens in our museums which show the formation of calculi in single kidneys, and in more than one case the ureter of a solitary kidney has become blocked with a calculus, so that death has resulted.

There is also reason to believe that the kidney of normal development which has undergone compensatory enlargement is peculiarly prone to become affected with Bright's disease, a fact which is attributed to the extra work which it has to do.* It is also probable that the presence of an inherent tendency to premature degeneration is an important factor.

The occurrence of a degenerate or infantile organ is by itself an indication of a tendency to easy degeneration on the part of the remaining kidney. The degeneration of one kidney must be

* *Vide* Drs. Fagge and Pye-Smith 'Principles and Practice of Medicine,' ed. 1, vol. ii, p. 390.

regarded as a stigma, in which all the organs are to some extent implicated, and most of all those in closest physiological correlation with the diseased organ. Though the opposite kidney is therefore the organ most liable to share in the degeneration, it may not be the only organ affected. Indeed, some other organ may be the only one to suffer. Thus Dr. Tweedy once exhibited an enlarged single left kidney taken from the body of a woman, aged 30 years, in whom no trace of kidney could be found on the right side. Yet the patient died from cirrhosis of the *liver* followed by peritonitis, "and the cause of death was in no way connected with the absence of the right kidney."

For similar reasons single kidneys seem to be peculiarly liable to become cancerous. An example of this was reported by Gœcke at a meeting of the Cologne Surgical Society.* In referring to three cases of defective development of single kidneys, he mentioned that in one the left kidney was rudimentary and fibrous, but the right was distinctly enlarged, and was almost completely embedded in a malignant tumour, which consisted partly of blood-vessels, partly of fibrous tissue, and partly of endothelium.

Another instance is given by Dr. Manby† of the occurrence of cancer in one kidney, the other being pre-natally absent. An interesting circumstance in connection with this case is that the patient was advised to have the kidney removed, but refused, and not until after death was it found that he possessed but one.

Arrest of development of the arterial system and of **both kidneys**, giving rise to diffuse sclerous nephritis, is mentioned by Senator.‡ He says that attention was first drawn to this condition by Besançon in 1889, and that Poillon and Lancereaux have also published examples. But, as a fact, Wilks and Moxon, in their work on 'Pathological Anatomy,' written in 1875 (p. 498), were fully aware that defective development constituted "an important predisposing cause of chronic insidious disease of the kidney in early life." There may be no indication of what is amiss until acute uræmia sets in and leads to speedy and inevitable death. This apparently most often occurs in youths and young adults, usually in chlorotic girls, and after death the kidneys are found to be of small size, or, at any rate, are not enlarged.

In some of these cases it is amazing how little kidney substance is needed to maintain life. Thus in a patient seen by Dr. Glover

* 'Deutsch. med. Wochens.,' 1897, vol. xxiii, p. 53.

† 'Lancet,' 1885, vol. i, p. 661.

‡ "Die Erkrankungen der Nieren," 'Spec. Path. u. Ther. Nothnagel,' 1899, Bd. xix, Th. i, S. 254.

Lyon,* a youth, aged 16 years, but looking not older than ten (general infantilism), the kidneys contained "certainly not more than one twentieth of the normal kidney substance available." The left kidney was represented by a piece of fibrous tissue less than $\frac{1}{4}$ in. (6.35 mm.) thick by $\frac{3}{4}$ in. (19 mm.) long. The right kidney was "extremely atrophied," and its renal substance was from $1\frac{1}{2}$ to $\frac{3}{4}$ in. (2 to 4 cm.) thick.

On rare occasions a baby may apparently be born with Bright's disease, as in Dr. Ashby's case,† where dropsy and defective secretion of urine were noticed on the second day after birth, and the child died in uræmic convulsions at the age of one month. The kidneys were lobulated, and resembled "large white" kidneys, and epithelial, peri-globular, and interstitial changes were found.

Sometimes the Bright's disease of children is definitely of the interstitial variety.‡ It is not possible to say that the Bright's disease of early childhood is invariably the result of an initial defect of development, though when the kidneys are found relatively small it may be assumed that such was the case.§

The Bright's disease of early infancy may be one of the causes of sudden death, as in the following instance, for which we are indebted to Dr. Murrell, of Reading. Dr. Murrell was asked to see a female child, aged 1 month, who had been found dead in bed. It was apparently healthy at the time of birth, and was breast-fed and thriving until the day before it died. It had no dropsy, was not fretful, nor unusually drowsy. The only indication that there was anything amiss was on the day before its death, when it was noticed that its cry was rather feeble. At 5 a.m. the mother awoke and found that the baby was breathing naturally, but three hours afterwards, when she began to get up, it was dead.

At the *post-mortem* examination we found the pleuritic and peritoneal fluids in excess and blood-stained. The supra-renal bodies were also slightly distended with effused blood. The heart and blood-vessels were normal, except for a few minute patches of atheroma in the aorta, and no other organ was diseased save the kidneys. The kidneys together weighed only 6.5 gm. They were good examples of the mottled form of Bright's disease, and on microscopic examination showed degeneration of such mixed kind

* 'Lancet,' 1901, vol. i, p. 102.

† *Ibid.*, 1901, vol. i, p. 296.

‡ Drs. Ashby and Wright, 'Diseases of Children,' p. 639; *vide* also Professor Hirsch, 'American Journ. of Medical Sciences,' vol. cxxvii, 1904, p. 1056.

§ As, for example, in Dr. Hall's case of a girl of eight, in whom the kidneys were of the mottled variety, but so small that each weighed less than one ounce (28 gm.).

that it seemed impossible to pitch upon one tissue as more implicated than another. A drawing of the section is given on p. 311.

There had been no sign of syphilis in either the child or its parents. The father was a drunkard, but the mother was abstemious.

An instance of unilateral Bright's disease apparently consecutive to infantilism is given by Mr. Pick,* in a paper entitled "Granular Degeneration of the Kidney the Result of Malnutrition from Malformation of the Renal Artery," in a man, aged 48 years. "The right renal artery terminated an inch (2·5 cm) from the aorta in a *cul-de-sac*, from which are given off two minute branches" to the kidney. This right kidney weighed 6 drms. The other kidney was healthy. Pick conjectured that the granular degeneration was produced in a similar way to the fibrosis of old age, *i. e.* by malnutrition from defective blood supply.

But, oddly enough, in a similar case recorded by Dr. Moxon,† an exactly opposite explanation was given. This was a case in which one kidney was large white and the other was normal, though the renal artery leading to the sound organ was plugged by an old clot. It was Dr. Moxon's opinion that the cutting off of the blood supply from the healthy kidney had prevented it sharing in the disease.

Whatever the explanation of the latter case may be, it seems certain that the degeneration of the kidney in Mr. Pick's case could not have been due to malnutrition, but rather to some primary defect in the development of the organ—infantilism in fact—and that this had led to the premature senility and to Bright's disease.

In a case reported by Sir Wm. Broadbent‡ one kidney was only 3 cm. long and was generally undeveloped, while the other was small and granular. The suprarenal capsule of the former kidney was also exceedingly small.

Sometimes the kidneys are lobulated—not that slight lobulation which is so often found on *post-mortem* examination, but the deep subdivisions which indicate a true pre-natal malformation. An instance of this is recorded by Dr. Murchison.§ It occurred in a youth, aged 18 years, whose case is described as one of "atrophied kidneys causing fatal uræmia." The kidneys had "more the

* 'Trans. Path. Soc.,' vol. xix, 1869, p. 281.

† *Ibid.*, vol. xix, 1869, p. 265.

‡ *Ibid.*, vol. xvi, 1866, p. 166.

§ *Ibid.*, vol. xxii, 1872, p. 177.

appearance of the permanent foetal structure, or that of the kidneys of some lower animal."

Another example is given by Dr. Kennedy.* A child died in convulsions on the seventeenth day after birth. The kidneys were found to be fibrous, and to contain many small cysts. They were also divided into three distinct lobes, and were scored with numerous lesser sulci. There was clearly degeneration consecutive to a failure of development.

In another interesting case a boy, aged 12 years, who was to undergo treatment for hyperplasia of the gums, showed symptoms of granular kidneys, and died from mæmia. His kidneys were found to be distorted by deep furrows, but were not granular. The left was also about twice the size of the right, and the lower half of the right was a mere knob of fibrous tissue. The heart was greatly enlarged, and there was widespread arterial sclerosis.

In a case reported by Dr. Jennett† there was "cirrhosis of the kidneys associated with congenital atrophy and malformation of the organ." The patient was a woman, aged 28 years. The left kidney weighed less than 1 oz. (28 gm.) and the right 2½ oz. (70 gm.).

A good example is also mentioned by Wilks and Moxon‡ in a young man who died from albuminuria, and who was found to possess but two pyramids in each kidney. The kidneys themselves were very small, and had that granular and contracted appearance which is characteristic of the small kidney of chronic Bright's disease.

Of 2610 *post-mortem* examinations made at the Middlesex Hospital there was found but one instance of misplaced kidney. This occurred in a lad, aged 19 years, who had died from chronic Bright's disease. Mr. Henry Morris,§ who records this fact, also says that out of nineteen cases of malformation, four were atrophied from disease.

It seems pretty evident that defective development of the kidney or kidneys, whether pre-natal or post-natal, is peculiarly liable to pass on into degeneration. In other words a persistently infantile state of the kidney hastens the onset of senile decay—senilism is prone to supervene upon infantilism.

* 'New York Med. Journ,' 1891, p. 335.

† 'Glasgow Med. Journ.,' vol. xxxi, p. 40.

‡ 'Pathology,' ed. 2, p. 498.

§ 'Surgical Diseases of Kidneys and Ureter,' ed. 1, p. 18.

V

PREMATURE SENILITY OR SENILISM OF THE KIDNEY— PRIMARY BRIGHT'S DISEASE

The degenerations of the kidney and liver have many points of resemblance. The *varieties* of primary Bright's disease are determined, in the main, by the age of onset and by the character of the tissue first affected. Inflammation, or nephritis, is to be distinguished from degeneration, or true Bright's disease. The small white kidney is probably a degenerated infantile kidney. The *causes* are toxins as a rule. There may be two or more causes acting together. The toxins are probably never the sole factors. Pregnancy apparently only precipitates the degeneration. Bright's disease occasionally occurs in an *hereditary* form. Its course is progressive and probably interrupted. It is *associated* chiefly with arterial fibrosis and with cirrhosis of the liver. The disease consists in a steady deterioration, starting sometimes in one structure, and spreading with more or less rapidity to the whole organ. Treatment mainly consists in the application of those sanitary measures which ordinarily tend to prolong life.

Comparison of Primary Bright's Disease with the Cirrheses of the Liver.

It is now recognised that the connection between the different forms of degenerations of the kidney and of the liver is much closer than was realised twenty years ago. This connection is, indeed, very intimate. To begin with, if there are two chief divisions of cirrhosis, that is, the large or "hypertrophic" and the small or atrophic, so also is there a large kidney of chronic Bright's disease and a small kidney.

The liver in hypertrophic cirrhosis is a big, smooth organ, occurring, as a rule, early in life, and is distinguished by proliferation of its special cells or parenchyma rather than by any great excess of fibrous tissue. But later on the liver-cells become fatty, the fibrous tissue encircling the lobules increases and gradually closes in, causing the liver to shrink, and in extreme cases (but this is very doubtful) to become atrophic.

So also is it with the "hypertrophied" or large white kidney of chronic Bright's disease. This, too, is a big, smooth organ, owing its size to proliferation of its constituent secretory cells, so

that the disease with which it is affected has received the name of "parenchymatous nephritis." But along with this cellular proliferation there is increase of fibrous tissue, which, it is thought, in course of time so shrinks the organ as to render it ultimately small, granular, and fibrous. The large white kidney is also a disease of early life, and, to a large extent, owes its colour to fatty degeneration of its epithelium.

Now let us turn to the small form of cirrhosis and of Bright's disease, and here, too, we shall see a very close similarity. In each case the distinguishing feature is the increase of interstitial fibrous tissue, causing the organ to become granular and contracted. Indeed, it would be quite as correct to term the ordinary hobnailed liver a granular and contracted liver as it is to apply that designation to the kidney. Moreover, in both cases the granules which stand up as elevations on the surface are the parts least damaged, for they are squeezed up between the meshes of the fibrous tissue. Both are senile diseases, or, more strictly speaking, usually occur at a time of life when natural senile changes are beginning. Both have alcohol as one of their causes, though they may set in without any definite cause and remain latent for long periods of time. Moreover, they often occur together.

There are many other ways in which they resemble one another, as will appear later on. Enough, however, has been said to show that their resemblances are more than superficial, but, on the contrary, indicate that there is some deep-seated relation between them.

Varieties.

Bright's disease may be divided into varieties dependent upon the rapidity of the course, the age of the patient, and the nature of the tissue first affected.

Rapidity of course.—The disorder may be acute, subacute, or chronic. Care must be taken not to confuse acute nephritis with acute Bright's disease. This distinction will be referred to farther on.

Age affects the character of Bright's disease by impressing upon it the peculiar features of the particular time of life at which the affection begins.

Regarded from this point of view there are at least five types of chronic Bright's disease :

(1) Pre-natal cystic form.

(2) Infantile and juvenile forms, comprising the small white and the mottled kidneys.

(3) The large white kidney or hyperplasic form of early manhood.

(4) The atrophic or cirrhotic form which occurs between forty and sixty.

(5) The senile form, on the borderland between the physiological and the pathological.

The following is a convenient classification of the diseases which are often included under the name of Bright's disease :

I. Nephritis or Inflammation.

(1) *Acute* or toxic, due to temporary intoxication with the toxin of scarlet fever, or other infective fever, or with cantharides, lead or alcohol.

(2) *Subacute and chronic* : (a) Suppurative, (b) tuberculous.

II. Bright's Disease or Degeneration.

(1) Degenerative hyperplasia or degeneration with overgrowth—the large white kidney.

(2) Intermediate :

(a) The mottled kidney.

(b) The non-granular interstitial form.

(c) The contracted white kidney (?).

(3) Senilism, or atrophic degeneration—the granular contracted kidney :

(a) Primary.

(b) Secondary.

(4) Cystic :

(a) Of pre-natal origin.

(b) Of post-natal origin.

(5) Amyloid.

(6) Senile.

Some of these varieties must now be more fully dealt with.

I. Nephritis.

It is very necessary to distinguish between acute nephritis and acute Bright's disease, a point which is insisted upon by Dr. Bradford.* Acute nephritis is essentially toxic and symptomatic,

* "Bright's Disease from a Clinical Standpoint," 'Lancet,' 1903, vol. ii, p. 2

and is the reaction of the kidney to some poison circulating within it. So soon as this poison ceases to circulate the inflammation subsides. But before subsiding it occasionally starts into activity that train of symptoms and alterations of structure which constitute acute or chronic Bright's disease.

Such a nephritis is comparable with the hepatitis or congestion of the liver which may be produced under similar circumstances. Just as we may have jaundice with tenderness of the liver started by the influenza toxin, and giving rise to what is commonly and absurdly termed a "chill on the liver," so may the scarlatina toxin give rise to albuminuria, hæmaturia, renal tenderness, and other signs of "chill on the kidneys." It is of no detriment to our comparison that in one case it is the secretion of bile which is interfered with, and in the other secretion of the watery elements of urine, or that the consequences of the one disease may be more serious than the consequences of the other. They are both alike intoxications, and are, as a rule, evanescent, but occasionally may be the beginning of degeneration.

II. Bright's Disease

Probably no chapter in pathology has undergone more discussion than that on the forms of Bright's disease, and even now it is very far from being ended. For this there are several reasons. Though it is possible to pick out certain types which stand out more or less conspicuously from all the rest, they are not in reality clearly marked off into separate diseases. Bright's disease is, in fact, one disease, but its manifestations are determined by a variety of circumstances, such as age, sex, the nature of the agent which starts it into activity, and the constitution or idiosyncrasy of the individual. Considerable difficulty also arises from the fact that Bright's disease may have a long latent period, so that the form of disease ultimately coming under observation may be very different from the original pattern.

Another source of difficulty consists in the fact that a kidney affected with chronic Bright's disease is, like all degenerated organs, vulnerable to attacks of bacteria, and the inflammation which they set up may appear again and again, so that at the end we cannot say exactly what is due to the original Bright's disease and what to the attacks of nephritis which have passed over it. Hence it can be understood that "considerable difficulty is often experienced in correctly placing some forms of chronic Bright's disease" (Dr. Bradford).

Then it has not yet been determined conclusively whether a large white kidney ever contracts either into the small white or into the small red, granular organ.

One possible source of misconception may also proceed from the circumstance that the kidney affected may not have been of ordinary size at the beginning. It may have been undeveloped or infantile. Now we know that an organ which does not develop at a proper rate is prone to undergo early degeneration. The change, moreover, sets in at a fairly early age, and is usually of the nature of a degenerative hyperplasia. But owing to the original small size of the organ we should not expect the degenerated kidney to be a big kidney.* Apparently of such a kind is the "*small white kidney*" of Rose Bradford. This form of Bright's disease has a long, latent course, occurs at an early age—"frequently under thirty, and not uncommonly under twenty-five years"—is often not attended with enlargement of the heart or fibrosis of the arteries or with œdema, has no known cause, and gives rise to a pale kidney of no great size, showing both fibrous and parenchymatous changes. The disease is, according to Dr. Bradford, a distinct pathological and clinical entity.

Senile Kidneys.

Another form which it is important to notice is the kidney which occurs at the end of life, and is termed the "senile kidney." "These kidneys are often markedly interstitial. There is a good deal of fatty and cellular degeneration, giving the surface a mottled appearance; but they need not necessarily be granular, and are usually large."† But there is another form of senile kidney of a kind usually referred to by that name, and that is the wasted kidney, which is often found in old men who have had no signs of Bright's disease. It may be fairly smooth on the surface, but is tough and fibrous and adherent to its capsule. It is not necessarily associated with any generalised sclerosis of the arteries. A good example is given on p. 311.

Apparently closely allied to this is the "*arterio-sclerotic atrophy*" first described by Ziegler.‡ In this form, too, the sclerosis may be confined to the kidney.

* Such a kidney is pictured on p. 311.

† Dr. Samuel West, "Lettsomian Lectures on some of the Clinical Aspects of Granular Kidney," 'Lancet,' 1899, vol. i, p. 351.

‡ 'Lehrbuch der speciellen Pathologischen Anatomie,' 1902, p. 788.

Clinical.

Among the *causes* of Bright's disease are certain toxins, chiefly those of scarlet fever, of syphilis, of wine, as well as gout and lead.

Dr. Hale White,* as the result of inquiries into the origin of chronic Bright's disease, concludes that scarlet fever is not nearly so important as is usually thought. Caiger found that scarlet fever gave rise to symptoms of tubal nephritis in only 2·8 per cent. of cases, and that very few of these became chronic.

It seems pretty clear that if we regard every instance of Bright's disease as the product of one cause, and one alone, we shall be wrong in the majority of cases. When a patient late in life is afflicted with the symptoms of granular kidney, the disease may have had its beginning in some early nephritis, the result of an attack of scarlet fever; later on, a too free indulgence in alcohol and in hearty eating may contribute their quota. But not until he has passed his prime do actual symptoms of kidney disease appear, and gradually separate themselves from the discomfort, the aches and pains, and the many petty ailments which are the outcome of high arterial tension, and of many years of over-eating and over-drinking.

So, in the same way, there is very little doubt that syphilis, lead, and gout do not so much originate Bright's disease as excite it into activity when it already exists in a smouldering or latent condition.

It is the opinion of Dr. Samuel West† that, though both gout and lead may produce chronic changes in the kidney, neither causes granular kidney. He concludes that patients whose kidneys are unsound are especially liable to suffer from the effects of lead, of gout, or of both. He would put the kidney disease first, and regard it as the cause of the manifestation of gout or of plumbism, and not as an effect, as is usually done.

But there are cases of Bright's disease for which it is impossible to find any cause. Generally speaking, the earlier in life the disease appears the more difficult is it to trace its causation. It is, for example, often impossible to assign any cause for the Bright's disease which begins in the foetus, or first shows itself in infancy, but later on we begin to suspect the influence of scarlet fever, syphilis, lead, alcohol.

Nevertheless, in adults alcohol, gout, and lead are not the real

* 'Clinical Journal,' vol. xxiv, 1904, p. 134.

† 'The Practitioner,' "Gout Number," vol. lxxi, 1903, p. 34.

causes of the complaint, but are mere factors in causation. We should still have chronic Bright's disease with us even though alcohol and other exciting causes could be swept away, for it occurs in the lower animals, in whom no suspicion of such causes exists. Moreover, some individuals may saturate their bodies with one or all of these poisons and yet live to a good old age, and die without any trace of kidney degeneration. It is therefore evident that, though of great effect, they are not the only factors.

Pregnancy.

One of the most knotty subjects in the department of obstetrics is the pathology of albuminuria in pregnancy. An interesting discussion of this question took place at a recent annual meeting of the British Medical Association.* The discussion was opened by Dr. Boxall, who directed attention to certain clinical points upon which most observers are agreed, some of which bear upon our subject. These are, first, that "not only is kidney inadequacy likely to arise in the course of pregnancy, but in women who are the subjects of chronic nephritis the disease is especially liable to take on an acute form when pregnancy supervenes." Secondly, "albuminuria is more likely to occur in women pregnant for the first time." Eclampsia occurs five times more often in primiparae than in multiparae (Schanta, quoted by Professor Byers). Thirdly, "the liability to albuminuria and to aggravation of the disease increases as pregnancy advances." Fourthly, "at the termination of the pregnancy the albuminuria almost invariably tends to subside." Fifthly, other organs are liable to share in the disturbance, and of these none is more commonly or more seriously affected than the liver.

Of the many explanations brought forward to account for these important facts two are now held in especial favour. One is to the effect that there is a disturbance of metabolism and of excretion during pregnancy, which is aggravated by high arterial tension and by the intra-abdominal pressure of the swelling uterus. The other explanation is that toxins are formed during the course of pregnancy, and that the whole process is either one of auto-intoxication pure and simple, or is combined with the semi-physiological factors just mentioned.

But there are many difficulties in accepting these views, not the least being lack of evidence of their existence. Thus it is more

* 'Brit. Med. Journ.,' 1905, vol. i, p. 715.

than suspected that the high arterial pressure referred to is the consequence rather than the cause of kidney disturbance.

Drs. Stengel and Starton,* as the result of a careful investigation into the effects of pregnancy upon the cardio-arterial system of some seventy women, came to the conclusion that, despite the embarrassment of the heart, which may be supposed to result from an increase in the total quantity of blood, and in spite of pressure on the abdomen and thorax, it is doubtful whether there is any real increase in the work of the heart. Moreover, if such increase occurs it is inconsiderable. In regard to the intoxication theory, it need only be said that no toxin has ever been found.

The view held here of this occurrence of albuminuria or of Bright's disease in pregnancy is that it must be classed with other diseases, such as osteomalacia, pernicious anæmia, diabetes, leucæmia, and acute yellow atrophy, which are induced or aggravated by the occurrence of pregnancy, and that no explanation can be regarded as satisfactory which does not cover them all.

Pregnancy, as we have seen, has a rejuvenating effect on the body, causing it to improve in nutrition and to resist the encroachments of bacteria. But it is of the very essence of the disorder senilism that the senile change should be premature, and the more premature it is the greater the disease. Hence anything which has the effect of making the body virtually younger, if only for a season, would necessarily act inimically upon any premature degeneration that might be going on within it. When pregnancy induces Bright's disease we suppose that there was already some such unsoundness or latent instability, and the pregnancy does no more than precipitate a disaster already impending.

Such a view as this is in accordance with the facts that albuminuria gets worse as pregnancy goes on, ceases when the reaction of the period of lactation sets in, and is most prone to occur in a first pregnancy, when the predisposition or latent weakness is most likely to be first brought out, the successful passage through the ordeal of pregnancy being regarded as proof that there is no strong tendency to degeneration.

During the discussion on Dr. Boxall's paper, referred to above, Dr. John Campbell, of Belfast, pointed out that in many instances of puerperal eclampsia there has been a history of the occurrence of albuminuria or even of nephritis before marriage, showing the existence either of latent Bright's disease or of a strong proclivity to kidney degeneration. He also alluded to the tendency for

* 'University of Pennsylvania Med. Bull.,' vol. xvii, 1904, p. 202.

eclampsia to occur in different members of the same family. Other corroborative items forthcoming at the same meeting were that of the special tendency for eclampsia to set in in unmarried as distinguished from married primiparæ noticed by Dr. Draper and attributed to mental strain ; and the tendency to occur in certain districts in preference to other remarked by Prof. Byers. Prof. Byers also said that a twin pregnancy is much more liable to be associated with eclampsia than is ordinary pregnancy, the difference being in the one case as 1 to 13, while in the other it is as 1 to 80. Of course the significance of this point lies in the fact that twins are of the nature of a congenital variation, and would therefore be more prone to be associated with another variation such as we suppose senilism to be. Drs. Gancher and Sergent,* who have studied the subject with great thoroughness, find that the albuminuria of pregnancy usually returns with each succeeding child and leads to permanent kidney disease. They regard it as probable that in many cases the disease exists in a latent form in the intervening periods. Anatomically the kidneys may be of the small, red, microcystic kind, or large white, but there is always increase of interstitial fibrous tissue and adherence of the capsules. Islands of fibrosis also occur.

Koblanck† traced out the subsequent histories of seventy-seven cases of albuminuria of pregnancy, and found that five of them, or 6·5 per cent., afterwards suffered from chronic Bright's disease.

In a case published by Dr. Bar‡ the patient, aged 19 years, died from eclampsia in her first pregnancy. The left kidney was small, cystic, and useless ; the right was very big, and affected with advanced tubal "nephritis." It seems pretty evident that there was ante-natal maldevelopment of one kidney, that there had been for a long time latent degeneration of the other, and that the occurrence of pregnancy had precipitated its downfall.

Hereditv.

A case is described by Brill and Libman§ in which a girl of 14 died from chronic idiopathic Bright's disease. After death the kidneys were found to be small, red, granular ; there was extensive arterial sclerosis (endarteritis obliterans), an indurated pancreas,

* 'Revue de Méd.,' Tome xxi, 1901, p. 1.

† Quoted by Dr. Blacker, "Albuminuria of Pregnancy," 'Lancet,' 1905, vol. ii, p. 1822.

‡ 'Bull. Soc. Obstét. de Paris,' Tome ii, 1899, p. 126.

§ 'Journ. Experiment. Med.,' vol. iv, 1899, p. 555.

brown induration of the lungs with moderate increase of connective tissue, thickening of the capsule of the liver with slight increase of interlobular connective tissue, and thickening of the capsule of the spleen. There were twelve other children in the family, six of whom died young from unknown causes, while a sister of nineteen was suffering from advanced chronic interstitial Bright's disease.

Bernhard* quotes a case described by Furbinger in which two young children, brother and sister, died with typical granular kidneys of unknown cause.

Dr. A. V. Meigs† mentions the occurrence of no less than five instances of primary Bright's disease in one family, consisting of father, son, and three daughters.

Dr. Dickinson‡ showed the Pathological Society of London a granular "kidney from a case in which albuminuria was hereditary." One of the relatives died from albuminuria, complicated with diabetes, and there was a history of hereditary transmission running back through four generations.

Cases of hereditary albuminuria, due apparently to "interstitial nephritis," have also been published by Dr. Francis Hawkins§ and others. Dr. Fieux|| says that the hereditary albuminuria of children sometimes constitutes a serious predisposition to Bright's disease.

In another example of hereditary transmission¶ the mother suffered from interstitial Bright's disease, of puerperal origin, which was verified at a *post-mortem* examination. Her two children died at the respective ages of eighteen months and two years, and in both cases the kidneys were found to be small and fibrous, apparently the result of degeneration acting upon undeveloped organs. Nothing is said of the presence of syphilis.

This case is, to all appearance, one of senilism in the mother transmitted in the form of infantilism to the children, and seems to be a striking example of the way in which these extremes meet.

But probably the most convincing instance of heredity is furnished by Tyson,** who says: "I was consulted in 1880 by a gentleman who had granular kidneys, and was at the time thirty years old. The disease was discovered in 1880 and he died in 1898. His father and mother both died of Bright's disease, aged fifty-six and

* 'Berlin. klin. Wochenschr.,' vol. xxxiv, 1897, p. 191.

† 'Trans. Coll. Phys. Philadelph.,' S. 3, vol. vi, 1883, p. 166.

‡ 'Trans. Path. Soc.,' vol. xl, 1889, p. 144.

§ 'Trans. Clin. Soc.,' vol. xxvi, 1893, p. 219.

|| 'Journ. de Méd.,' 1899, vol. xxix.

¶ Hellendall, 'Archiv f. Kinderheilk.,' Bd. xxii, 1897, S. 61.

** "Treatise on Bright's Disease and Diabetes," Philadelphia, 1881, p. 166

sixty-five respectively. The mother had convulsions. A maternal uncle died of Bright's disease when about sixty-four. A cousin, daughter of the above, died when about twenty-seven, of supposed Bright's disease, having had convulsions. A brother died in 1877 of Bright's disease, without convulsions, at the age of thirty-seven. Two children of this brother had Bright's disease when four and seven years of age. A second brother died in 1871, at the age of twenty-nine, with convulsions. A third brother died in 1892 of Bright's disease, aged thirty-eight. A fourth brother in 1880 was known to have had Bright's disease for about six years and has died since. A sister died of uræmia in 1890, at forty-four, having had Bright's disease for thirteen years. A brother died in 1897, aged forty-two, but not of Bright's disease, and a sister, aged fifty-seven, has as yet no signs of Bright's disease. Other members of the family, belonging to previous generations, died with symptoms which suggest Bright's disease. There is no gout in the family."

Course.

It is well known that the course run by chronic Bright's disease, especially in the granular form, is very insidious, so that perhaps nothing is known of its presence until a cerebral hæmorrhage or some defect of vision draws attention to the kidneys. It resembles cirrhosis of the liver in this respect, and also in the variations which takes place in its progress. Intermittence in the rate of progress is sometimes well shown in cystic disease.*

"Complete recovery is seldom seen when the disease has lasted many months, still more rarely when prolonged for years, but it is surprising how symptoms will sometimes subside and disappear, so that even after the patient has been water-logged and has had alarming uræmic attacks he yet recovers."†

The younger the patient affected with Bright's disease the more rapid is its progress (Dr. Hale White).

Associations.

Under normal conditions no organs are so closely connected with the kidneys as the cardio-vascular. Indeed, their association is so very close that it is the custom to look upon the *cardiac and arterial changes* as part and parcel of the disease of the kidneys. But as a

* Dr. H. Cooper Rose, 'Med.-Chir. Trans.,' vol. li, 1868, p. 167.

† Drs. Fagge and Pye-Smith, 'Text book of Medicine,' vol. ii, p. 643.

matter of fact, we are no more justified in taking this view than we are in regarding arterial sclerosis as an integral part of cirrhosis of the liver, of osteitis deformans, or of any other degeneration which often goes with it. Chronic Bright's disease can exist quite apart from arterial degeneration, and *vice versâ*, arterial degeneration can occur in a very advanced state apart from disease of the kidney.

Degeneration of the heart and arteries must, therefore, be dealt with in a separate chapter, and not be included under the heading of "Bright's disease."

The organ which comes next in order of physiological relations is the liver, and *cirrhosis of the liver* is consequently of frequent occurrence in chronic Bright's disease. But this association has already been considered in the chapter on the degenerations of the liver (p. 279).

The association of chronic Bright's disease with *errors of pre-natal development* has already been dealt with in the chapter on infantilism of the kidneys (p. 294).

Anatomy and Pathology.

Much of the difficulty which is associated with the study of Bright's disease arises from the widely different anatomical appearances of different specimens of the same clinical disease, and from the varying interpretations which have in consequence been put upon them. It is because of this divergence of form that the interstitial connective tissue, the capillary loops, the epithelium of the tubules, the capsule and the arterioles have each in turn been accused of being the starting-point or chief factor in the disease. And if to these we add the inner, the middle and external coats of the arteries, either of the kidneys or of the body at large, and ring the changes on these different parts, we may form a fairly accurate conception of the number of views brought forward to explain the pathology of Bright's disease.

Opinion of the present day tends to the conclusion that primary Bright's disease is more or less a mixture of all these different changes, sometimes one being predominant and sometimes another.* It is, therefore, recognised that while in the greater number of instances of Bright's disease the disorder may be termed "tubal," "glomerular," "interstitial," or "cystic," yet these forms are always more or less mixed, and in some case may so merge one into the

* *Vide* paper by Dr. Saundby, "Histology of Granular Kidney," 'Path. Soc. Trans.,' vol. xxxi, 1880, p. 148.

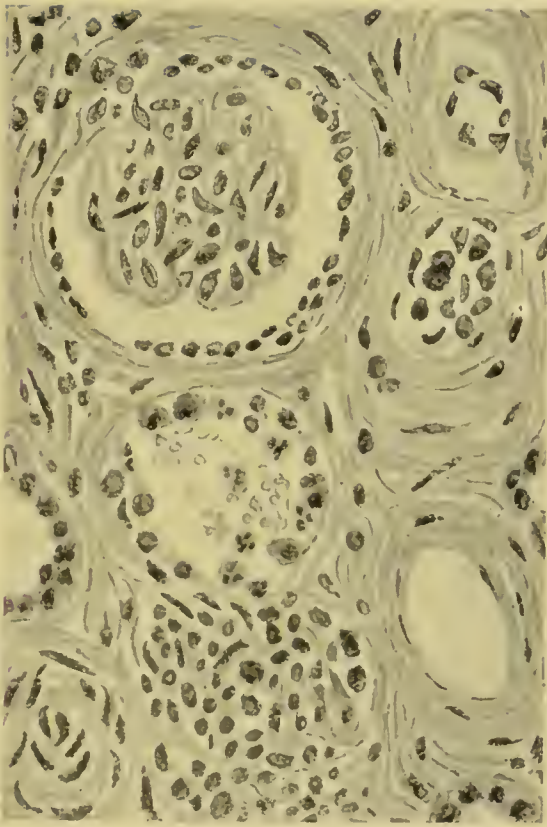


FIG. 5.—*Spontaneous Bright's disease of Rose Bradford type*: From a man, aged 21 years, who died from uræmia without previous symptoms (p. 303).

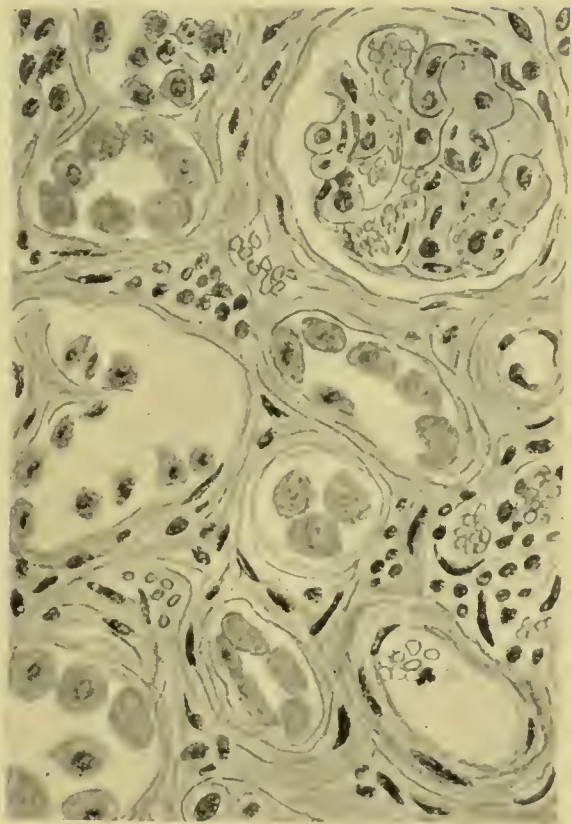


FIG. 6.—*Senile degeneration*: From a man, aged 78 years, who died from pernicious anæmia, and had shown no signs of kidney disease (p. 303).

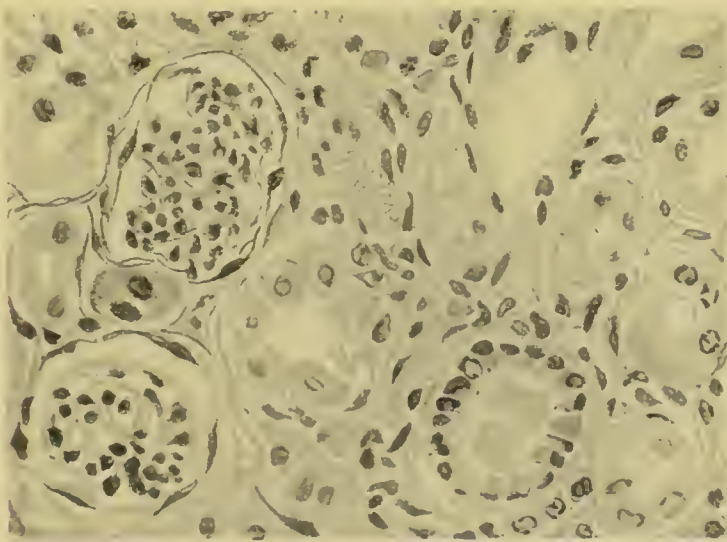


FIG. 7.—*Bright's disease of Rose Bradford type* From a baby, aged 1 month, who died suddenly without previous symptoms (p. 296).

The epithelial cells are losing their special characters and are proliferating and retrograding to a simpler or more rounded shape. Many phagocytes can be seen, and also fibroblasts in process of becoming new fibrous tissue.

other that it is impossible to say to which type a particular kidney belongs.

The changes in the kidney of Bright's disease are in every way analogons to those in the liver of cirrhosis. Seen under the low power of the microscope it is evident at a glance that the orderly arrangement of cells and fibres has been spoiled, and that the organ throughout is undergoing a change for the worse. Its organisation is giving place to disorganisation, structure to destruction, so that where before there were closely ranked tubules of co-ordinated cells and neat balls of capillary loops, now there is a disconnected medley of cells and cell *débris* and swollen, untidy tufts. The kidney is, in short, in process of reverting to its embryonic form.

This is borne out by further examination under a high power. In a typical kidney of Bright's disease of mixed form, such as we have just alluded to, the higher kinds of cells, particularly the epithelia of the tubules, are everywhere undergoing proliferation or molecular decay. Their cytoplasm becomes hazy, granular and fatty, and mixed among them are numbers of cells of embryonic type, mainly lymphocytes and fibroblasts, engaged in the work of absorption. These processes of absorption and multiplication may be seen in all their stages, but the final result to the cell is that nothing is left but a small round cell or a nearly denuded nucleus.

An important difference between the liver and the kidney, in cirrhosis and Bright's disease respectively, is that in the liver the bile-ducts do not form such definite tubes as do the renal tubules. In the liver the secretory cells are arranged outside or peripherally with respect to the canals, whereas in the kidney they are situated within the lumina of the tubules. Hence in the liver all those cells which have undergone simplification are disposed of in the organ. But in the kidney the tubules soon become filled with a granular *débris*, consisting of masses of broken-down or proliferating cells mixed with numbers of decaying phagocytes. These form plugs, which either choke the bores of the tubes or are washed out in the form of casts.

Degeneration is in some places shown more by increase in size than by granular and fatty changes. This is especially true of the flat cells of the pavement epithelium covering the glomerular tufts, which first become swollen, and so lose their especial qualities, and then proliferate, and, mixed with lymphocytes, help to fill and distend the Malpighian capsule. So full of simplified cells and lymphocytes may the capsules become that the blood and lymph

supply is cut off and their contents assume a swollen hyaline condition. In short, in every direction there may be seen a process of reduction of kidney tissue to a simpler state, the ultimate result being that the organ contains far more cells, though of less value. There is an increase in numbers, but a corresponding decrease in quality and in usefulness.

As in the case of the liver, the blood-vessels and the capsule also share in the general deterioration, and become increased in size, deformed and fibrous.

Treatment.

Nothing seems to be clearer than that the general treatment of chronic Bright's disease must be of a kind best calculated to preserve any man to a green old age.

A quiet life in a warm, equable climate; an unstimulating diet, in which the proteids are cut down to a physiological minimum; gentle, regular exercise, pleasant and congenial companions, and an atmosphere of hopeful contentment are all of importance. But we cannot do better than quote the words of Dr. Samuel West, who, in writing on the treatment of chronic Bright's disease,* says of its early stage: "The patients must live moderate, careful, and temperate lives, be properly clothed, avoid chills and exposure, keep their skin in good action, and the bowels regular. They must avoid alcohol, especially spirits, eschew dissipation of every kind, and live as much as possible in fresh air and sunlight. Even their recreations need not be seriously restricted, provided they are not such as lead to risky exposure or fatigue. Bathing, of course, in the open must be absolutely prohibited, so also fishing, so far as it involves wading, or shooting, except in fine weather, and hard hunting, but riding and all forms of gentle exercises, if chill and exposure and over-fatigue are avoided, may be allowed and are beneficial. The early stage spreads itself over many years, and the strain of the disease is usually not felt until the age of forty or fifty years. Till then, or till other symptoms develop, with care and good management life may be active and enjoyable both in work and play. During the early stage, then, the general health should be maintained in every way by appropriate dieting, by avoiding exposure, overwork and worry, by fresh air and regulated exercise. All this is compatible with an ordinary life, and though medical supervision and care are requisite, this need not be in special institutions or particular places."

* 'Lancet,' 1906, vol. i, p. 1027.

VI

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF THE NERVOUS SYSTEM

The diseases of the nervous system are marked by special features founded upon peculiarities of normal function and structure, but are fundamentally similar to the undergrowths and overgrowths, infantilisms and senilisms of the kidneys, liver and other organs.

Overgrowth of the brain is met with in genius; **undergrowth** gives rise to defects of quantity rather than of quality.

Infantilism is best shown in defective development of the brain, or microcephaly. It is apt to result in premature degeneration. This consecutive senilism accounts for such diseases as amaurotic family idiocy and dementia præcox. Some developmental diseases are due to various causes and are minor variations; others are occult in origin, and are major variations. Tabes and dementia paralytica are good examples of minor variation.

Introduction.

IN dealing with the subjects of infantilism and senilism of the nervous system it is requisite that we should first distinguish as clearly as possible between insanity and degeneration. This is just as important as it is to differentiate between inflammation and degeneration. Like inflammation, insanity may be a temporary disturbance only. It is comparable with the nephritis which sometimes precedes Bright's disease, or with the similar derangement of the liver preceding cirrhosis. Nephritis or hepatitis is equally an insanity, and may either be due to some external agent alone, or it may be a sign that degeneration is taking place, and has rendered the organ so susceptible to the action of such agent that the inflammation seems to be spontaneous. So also mental insanity may either be almost the sole result of some outward circumstance, or the first sign of degeneration. In the former event it may entirely disappear; in the latter it is followed by dementia. Hence the causes of insanity are also the causes of dementia. Furthermore, the causes of dementia in the parent are, generally speaking, the causes of amentia in the offspring.

The diseases which are included under the head of defective

development and premature degeneration of the nervous system stand out very conspicuously from all other developmental diseases.

In the first place no other organ in the body is so many-sided as is that comprising the nervous system. This diversity is due to the fact that not only is it the seat of consciousness, of perception, of intelligence, of judgment, but it presides over and regulates every organ in the body. It is the organ of the mind ; the register of sensation ; the regulator of motion. The brain and spinal cord are subdivided into a number of different physiological tracts or areas ; and just as in the kidney or liver senilism may start in any one physiological department, and may remain more or less confined to it, so is it with the nervous system. Heredity, age, sex, locality, each plays its part, with the result that the degenerative diseases of the nervous system are of great variety, some more or less closely resembling one another, others standing more or less apart, but differing only in the same way and to the same degree that the normal structure or function differs.

The developmental disorders of the nervous system illustrate, in a very remarkable way, the socialistic properties possessed by combinations of cells in the habit of working together. The nervous system, like the lymphatic system, may be regarded as one complex organ, or as a number of co-ordinated organs. These conglomerated organs do not develop simultaneously, but more or less independently, one being a little in advance of another. Moreover there is no equality of change during the declining periods of development. The old man does not lose nerve power equally. His reflexes may be the first to become sluggish, or he may fail in his locomotor nervous mechanism, or in his bladder control. So also in presenile degeneration or senilism. The toxin or other *materies morbi* never affects all parts alike, but is invariably partial, preferring one system to another system ; but often when at first confined to one system, and the degeneration in course of time extends to another, it may be observed that the system generally implicated is that which is its nearest ally under normal conditions. The degeneration, in other words, is most likely to extend to the sub-organ correlated to the one which is first affected. This process of involvement by association or correlation is well exemplified in progressive muscular atrophy. The degeneration of motor root cells in the anterior horns of the spinal cord is usually complicated with similar degeneration of corresponding motor cells in the medulla, giving rise to bulbar paralysis. Often there is also degeneration of the antero-lateral white tracts, producing amy-

trophic lateral sclerosis ; and, as a rare event, degeneration of afferent tracts of the posterior or postero-median column may lead to the supervention of symptoms of locomotor ataxy. Lastly, cases have been recorded in which the cerebral cortex has been involved, giving rise to general paralysis.

The *causes* of insanity constitute a compendium of the causes of degeneration in general. Mechanical injuries, fright and other emotional storms, moral shocks, mental excitement, disappointment, poverty, overwork, and that host of indefinite depressing conditions which we do little more than hint at as the causes of cancer, goitre, pernicious anaemia, and other degenerations, assume almost the definition and certainty with which we ordinarily regard such concrete causes as lead, syphilis, and alcohol. And this trio, again, while it sometimes affects one organ and sometimes another, shows a special partiality for the nervous system. It is with nerve degeneration as it is with the degeneration of other organs ; as a rule the causes are more or less complex. One cause seldom acts alone, but is usually fortified by another or by others. Thus "poverty, vice, crime become the indirect causes of insanity through an environment which tends directly to impair the general health."* Any of the less definite factors will have the more effect if its influence be exerted on an alcoholic or syphilitic subject, and *vice versâ*. Syphilis, alcohol, and lead are more potent when acting conjointly, and the same may be said of combinations of either of these with the depressing emotions or with other toxins. "The cause of insanity not infrequently has a direct bearing upon prognosis. A brief accidental exposure to a single toxic cause is favourable to recovery ; such, for instance, are the puerperal cases with confusional insanity, and the acute delirium which follows one bout of alcoholic indulgence. If a single and powerful cause be operative, such as a disappointment in love to a sensitive woman, the prognosis is better than if several causes, such as poverty, anxiety, and domestic bereavement, acted in conjunction."† Hence, not only are the varieties of degenerations of the nervous organs very great, but their causes are equally comprehensive. Each cause has its special affinity for some special region. Thus the degeneration produced by alcohol, arsenic or lead favours the peripheral nerves. Syphilis is central or cortical, and gives rise to dementia paralytica or to tabes, and so on. But this selective action is not invariable. Thus alcohol, in the form of acute alcoholism, may give rise to acute

* Dr. Robert Jones, 'Brit. Med. Journ.,' 1905, vol. ii, p. 1578.

† *Ibid.*

degeneration of cortical cells, and be a cause of dementia (Bonhofer and Trömmer, quoted by Mott).

As in the case of other organs the degree of derangement produced by any particular cause is not solely dependent on the quantity of that cause, but also, to a very large extent, upon the susceptibility of the organ. Hence violent emotion may so influence an individual with a susceptible liver as to give rise to a furred tongue, to a metallic taste, and to thick urine, and this "biliousness" may even last for a few days. But let the same cause act upon a susceptible brain, and the result is much more obvious. The insanity of the mind is far worse than the insanity of the body. The one we term a slight ailment; the other loosens the very keystone of the arch, and may lead to grave disaster, to suicide, murder, or to permanent deterioration of both mind and body.

Whatever may be said in this respect of the causes of degenerations of the nervous system may be said in principle of their *treatment*. On somewhat hazy, inconclusive grounds, we believe that those who live on a dry soil, in a bracing air, are less liable to cancer, Bright's disease, leukæmia, and other degenerative diseases, especially if busy with congenial pursuits, with sufficient leisure, and enjoying the advantages of a sunny sky, clean air, and cheerful society. But when we come to the treatment of insanity, we no longer speak of these means of cure with any diffidence whatever, but confidently assert, without hesitation, that these and the like are sanitary for the mind, whether or not they are sanitary for the body. And when a man is once insane, what more can we do for him than to put him in a big, roomy house in an open, breezy situation, with an ample garden and plenty of food, recreation and fresh air? The advantages of this treatment are rather accentuated than otherwise by the lack of suitable society, for if good results be obtained in spite of this serious drawback, what might not be done if this defect were removed?

So also with the *course* run by deteriorations of the nervous system, and with the effects of the different physiological epochs, especially puberty, the menopause, childbirth and lactation. We may sometimes have our doubt of the reality of their influence upon some other degenerations, but there is no question of their prime importance as factors in the production of certain brain diseases.

Then, again, remissions, which we have already remarked in the course of many other degenerations, are to be seen very plainly in mental states. This is clearly stated by Dr. Clouston, who says: "Periodicity, or a tendency to alternations of elevation and depres-

sion, is a very common characteristic of mental disease; it is much more marked when they are very hereditary than in any other case; and is in its essential nature the exaggerated or perverted physiological diurnal, menstrual, sexual, or seasonal periodicities of the healthy brain.”*

Dementia præcox, tabes, general paralysis, and, particularly, disseminated sclerosis, as well as other fibrous degenerations of the cerebro-spinal system, all show a tendency to spontaneous rhythmic changes, and these changes are sometimes very pronounced. General paralytics may, as Dr. Savage has pointed out, have an interval of sanity in which they are able to draw up a will, disposing of their property, and in other respects behaving with conspicuous intelligence. In disseminated sclerosis remissions are often quite as complete, so that Dr. Buzzard† and others look upon them as valuable diagnostic signs, of great help in separating disseminated sclerosis from hysterical paralysis. So also patients who suffer from tabes dorsalis, or from progressive muscular atrophy, are liable to intervals of quiescence or of improvement, so evident that often they are attributed to the use of some drug which they may happen to be taking at the time of their appearance. These intervals may last for months or even years, and if during any of them a patient die of some other complaint, he will be regarded as an instance of the cure of an incurable disease. Moreover, as a rare event, though the patient lives a life of ordinary length, the disease never does recur, but finally subsides and undergoes a spontaneous cure.

It is partly owing to this periodicity that the whole course of some of these maladies, and particularly of tabes, general paralysis, and disseminated sclerosis, is so variable. Thus a nerve system disease may smoulder on for years, and then suddenly light up into a blaze of great intensity, and these sudden augmentations may occur without any perceptible cause.‡ They remind one strongly of the sudden appearance of symptoms of acute yellow atrophy in a cirrhotic liver, or of acute Bright’s disease supervening upon the chronic form.

The duration of the mental insanities and degenerations varies exceedingly. A degeneration may be so acute as to simulate

* Dr. Clouston, ‘Mental Diseases,’ 6th ed., p. 242.

† “On Remissions and Relapses in Insular Sclerosis,” ‘Lancet,’ 1904, vol. ii, p. 131.

‡ Sir William Gowers, ‘Brit. Med. Journ.’ 1905, vol. i, p. 1; also “The Development of Acute Symptoms in the Course of Chronic Nerve Diseases,” Dr. James Taylor, ‘Polyclinic,’ 1904, p. 15.

meningitis (Professor Spiller). Insular sclerosis may end fatally in three months, or it may go on for twenty years or more (Ribbert), and much the same may be said of other nerve degenerations.

Any particular cause acting at one time of life may have very little effect, but acting at another its consequences may be disastrous. In other words, the appearance of insanity and of brain or cord deterioration is largely influenced by the epochs of life. This is especially shown in the insanity which shows itself during the physiological crises of *childbearing* and *childbirth*. Puerperal insanity is not due solely to the shock of parturition, though this circumstance has an important influence, for Drs. Batty Tuke and Clouston have shown that no less than 21 per cent. of the cases occur in unmarried women, or three times the proportion of illegitimate to legitimate births. But that shock, however produced, is not the only cause suggested by the fact that "during pregnancy the mental state of very many women is not quite normal."* Moreover, more than 50 per cent. do not take place until after the first week, when it may be supposed that the shock has lost its effects.

The climacteric of the *menopause* accounts for many cases of insanity in women, and it has been noticed that the neuropathic condition of periodic inebriety in women not infrequently occurs at the menstrual periods (Dr. Robert Jones).

We have attached much importance to the *association* of degenerations or of developmental defects with degeneration, and believe that such association proves a close relation between the diseases so connected. These associations occur more often in the case of some disorders than of others, but in no disease are they so marked as in the infantilisms and senilisms of the nervous system. So common are they that the very phrase "stigmata of degeneration" is often regarded as if it applied solely to affections of the nervous system. Everyone recognises that idiocy, imbecility or weak-mindedness often accompanies some pre-natal abnormality of the body, either personal or of family distribution, or some post-natal abnormality like epilepsy, diabetes, or defective development of sex. But degenerations of another kind frequently occur in the same individual side by side with nerve degeneration. Thus we shall, in another chapter, find that a patient who has pernicious anæmia is very likely to have with it combined degeneration of the spinal cord, and the same may be said of the leukæmic individual. Osteomalacia is also prone to be associated with some spinal cord

* Mr. F. StJohn Bullen, 'Hospital,' vol. xxvii, 1899, p. 195.

degeneration, and probably the same may be said of osteitis deformans. In all these cases, though one disease may favour the appearance of the other, it does not favour it to such an extent as to deserve the name of cause or effect. They run concurrently, the result of a similar "dyscrasia" affecting different organs, and are the result of correlation.

Structural.—We have seen that all those functional derangements or symptoms which characterise the true degenerations of the nervous system stand out in high relief, and the same may be said, and to a like degree, of structural characters. Nervous tissue contains the most highly organised cell elements in the body, and when these are reduced by degeneration to their elemental simplicity it necessarily follows that the change is very conspicuous. Just as the downfall of a big City magnate—some Jabez Balfour of finance—attracts the attention of a whole nation and has far-reaching consequences, whilst the ruin of a small shopkeeper has merely a local effect, so is it with the degeneration of the neuron, compared with the decay of less important cells, such as those of muscle or bone.

It has been pointed out by Dr. Mott* that the development of the nervous system "depends not so much upon an increase in number of the nervous units, but of their size by multiplication and complexity" of their processes. Cajal has shown that this growth in complexity is not only true of the development of the individual, but is also true of the development of the race. In old age the brain and spinal cord undergo, as a rule, changes in the direction of a reversal of development or regression. Thus the brain shrinks, so that, as Sir G. M. Humphry has pointed out, bone is sometimes deposited on the inside of the skull to make up for the loss of its contents. At the same time the convolutions become less raised or positively flattened, and the brain as a whole becomes tougher and more fibrous. Moreover, there is no boundary line between this senile brain and that found in the subjects of general paralysis or paralysis agitans. In brief, in the senile brain there is a regression of the neuron with a corresponding reduction in the number and length of its processes. Further, running side by side with this simplification of higher elements of brain-tissue there is an increase of low-class cells (lymphocytes, fibroblasts, etc.) and fibres, so that not only are the neurons of a more primitive type, but they are

* "Degeneration of the Neurone," 'Brit. Med. Journ.,' 1900, vol. i, p. 1522.

separated further from each other by the growth of intervening inert tissue.*

These changes of old age are also characteristic of the premature and exaggerated degeneration termed "senilism." The outstanding cell extensions, "those parts most remote from the trophic and genetic centre of the complex cell (neuron), degenerate. The process may be regarded as the inverse of development, the finer collaterals and terminal arborisations being the first to disappear."†

Dr. Mott goes on to show that Dr. Hughlings Jackson, writing in 1884, stated his belief that the diseases of the nervous system are reversals of evolution or dissolutions. They "commence in the structures latest developed, namely, the myelin sheath, and the terminal arborisations and collaterals of the neuron."

Excesses and Defects of the Growth of the Brain. Overgrowth.‡

Overgrowth of the brain probably accounts for many instances of precocious ability in children, and of exceptional talent, or of genius in adults. It may be partial or complete. When *partial*, its subjects show themselves singularly apt in certain directions, as in music, arithmetic, or in the knowledge of languages. When *complete* they excel, not only in one or two subjects, but in general intellectual capacity, far above that of their fellows.

In the former class we reckon Mozart, Mendelsohn, Beethoven, among musicians and composers, and Euclid and Newton among mathematicians. Certain men, accomplished in languages or in calculating powers, furnish other examples of extraordinary growth of some particular faculty of the brain.

Among those possessed of general brain overgrowth were Gladstone, John Stuart Mill, Cuvier, Abercrombie, Macanlay, and probably Bacon and Shakespeare. Some men have been as conspicuous for the size of their brains, or for the evidence of their intellectual capacity, as was Samson for the size and strength of his muscles. The average brain weight of an adult is 1390 gm. The brain of Cuvier weighed 1828·5 gm.; that of Daniel Webster

* Dr. Clouston says ('Brit. Med. Journ.,' 1898, vol. ii, p. 304) that in extreme old age, between seventy-five and eighty, the cell body appears granular, has fewer processes, many of its dendrites and gemmules having undergone atrophy or bulbous swelling, "the actual number of neurons in any given field of the microscope is fewer than in youth, just as is seen in brain sections from demented."

† 'Brit. Med. Journ.,' 1900, vol. i, p. 1522.

‡ Though not a disorder this is a biological extreme, and therefore a variation, and as such is put in here for the sake of completeness. It must be distinguished from macrocephaly, which is degenerative hyperplasia of the brain.

1807·3 grm.; of Abercrombie 1786 grm.; of Spurzheim 1559 grm.,* and of Turgenev 2012 grm.†

Undergrowth of the Brain.

It is by no means certain that morbid littleness of parts of the nervous system are always due, in the first place, to imperfect development. It is quite possible for development to continue to its usual limits, and for the defect to be primarily one of growth, so that trouble may arise, not from want of quality, but of quantity only, the organ failing from mere incapacity to respond to the calls made upon it.

Microcephalic idiocy is, probably, as a rule due to defective development of the brain. But this is perhaps not true of all microcephalic idiots, for apparently the condition is sometimes not an error of development but of growth. Thus, Dr. Langdon Down, referring to "a case of asymmetrical development of brain," says ‡ of the brain of the patient, a girl aged 17 years, idiotic from birth, and having an insane father, that "it was rather an arrest of growth than of development, as indicated by the complexity of the defective convolutions."

So also with so-called defective development of other parts of the nervous system. It is not unlikely that the affair may sometimes be one of undergrowth rather than of under-development, but we cannot find that any special observations have been made upon this point.

As a matter of fact we do not expect that dwarfism of the brain will present itself in such conspicuous forms as infantilism. It is well known that some men show no lack of wits though their brains are uncommonly small. Indeed the head may be so under-sized as to constitute a distinguishing feature, and yet the intelligence may be above rather than below the average. Thus Shelley and (it is said) Gambetta had small heads, yet they were emphatically not devoid of intelligence, but the reverse. There is, in short, plenty of evidence that the brain may be deficient in quantity but excellent in quality, and *vice versa*; and that up to a certain point the size of a brain is not the measure of its intellectual status but of its capacity, so that generally speaking the larger brain will both store and give out more work than the smaller brain.

* 'Anomalies and Curiosities of Medicine,' Drs. Gould and Pyle, p. 249.

† 'Medical Times and Gazette,' 1883, p. 500.

‡ 'Trans. Path. Soc., London,' vol. xx, 1869, p. 7.

Infantilism of the Nervous System.

The nervous system may be of defective development as a whole or in part. One or both of the cerebral hemispheres; a few convolutions; the cerebellum; the spinal cord; one or more nerve tracts; or some motor, sensory, or psychical area may alone be imperfect, and its function defective. The extent and variety of such developmental errors of the nervous system are probably almost as great as are those of the corresponding errors of all other parts of the body together. At the same time the structural alterations are often inconspicuous. They may be so slight that it is not possible to detect them, even on the closest visual examination, and yet they may be sufficient to disturb some important function, giving a twist to the body or mind or to the "character," which handicaps the individual throughout the whole of life. "Hemiplegia, sensory defects, imbecility, epilepsy in children, may be due to the arrest of development of cerebral cells without any change being apparent to the naked eye."* When these defects are pre-natal they are usually very pronounced, and have as much effect upon the mind as a club foot or a hare-lip has upon the body. Their results may be also altogether out of proportion to their degree, as when on the one hand the lack of development of an insignificant portion of the canal between the third and fourth ventricles gives rise to hydrocephalus, and on the other hand a serious deficiency of whole convolutions in some frontal lobe is apparently attended with no consequence whatever. But we are concerned now only with the defects which arise after birth, and these, as a rule, are much less pronounced than those which are pre-natal. Perhaps the best way of dealing with them is to take one form only, and that the worst, or at any rate, most comprehensive, and regard it as a sample of all the rest.

Defective Development of the Cerebral Hemispheres:

Microcephaly (see also p. 572).

Though microcephaly begins at any age of progressive development, there is an almost continuous series of transitional forms, from the normal fully developed human brain to the most extreme microcephaly (acephaly).

* Dr. Allen Starr, 'Med. Record,' vol. lxi, 1902.

Microcephaly is often *hereditary*, the heredity, of course, being invariably of the family kind.

In respect to *causation* neither syphilis nor alcohol seems to play an important, if any, part and the causes in general are occult.

It is often *associated* with encephalocele, porencephaly, hydrocephalus, and with other bodily deformities such as webbed fingers and anomalies of the auricles, teeth, sex organs. Dr. Langdon Down says that there have been several cases of *disseminated sclerosis* and *pseudo-hypertrophic paralysis* in combination with microcephaly.

We have now under our care a child with microcephalic idiocy, who shows a curious form of atavism. The hair is conspicuously red, though not one of the parents or grandparents has, or has had, red hair, and, so far as the parents know, none of their predecessors. The atavism, of course, consists in the fact that (there is reason to believe) the hair of primitive man was of a red or reddish colour.

One of the most interesting associations is defective development of the vault of the skull. Like all other correlated defects this is not of constant occurrence, though it is said to be noticed in more than half the number of cases. The ossification is then delayed to such an extent that there is a perfect adjustment between the degree of development of the bone and of the brain it encloses. It sometimes happens that ossification goes on in the membrane bones of the skull, exactly as if there were no microcephaly. In other words, though the brain is defective, there is no associated defect in development of the skull-cap. The result of this is that the ossifying membrane, being too big for the diminutive brain, falls together, so that a pleat or fold is formed where the membrane ossifies last, and as the microcephalic head is defective in breadth more than in length, it necessarily follows that the fold is longitudinal. More probably there is no actual fold of the membranes along the vertex, but such a general and uniform deficiency of *growth* that the actual surface area of the membrane keeps pace with that of the underlying brain. The consequence of this is that when ossification takes place and spreads along the membranes exactly as if the skull-cap were of its normal size, it encroaches on the membranous gap which ought to be left between the adjacent bones, and bone material is piled up into a ridge, obliterating the suture and welding the pieces together into a seamless case.

Anatomy.

M. Voisin, writing in 1874,* pointed out that the histological features of the brain of the microcephalic idiot are in all important respects identical with those of the infant, and this has now become a well-established fact.†

Degeneration Consecutive to Infantilism.

The microcephalic idiot is prone to degeneration of the nervous system, so that it is sometimes difficult to say whether he owes his idiocy more to defect of development, or to secondary degeneration, to amentia or to dementia. There seems to be all stages between the idiot with the large brain of fibrous hyperplasia, and the idiot who is microcephalic only; and it is particularly among intermediate cases that the difficulty of interpretation sometimes arises. Local degenerations are also prone to occur and to give rise to paralysis,‡ epilepsy, or to sensory defects.

Many instances of nerve disease which come under notice as degeneration are not primarily of that nature, but are based upon a prior defective development of the diseased organ.

These consecutive degenerations vary according to their situation and the time of life at which they appear. For example, progressive degeneration of the brain cortex in infancy extinguishes function while it is yet only flickering, and therefore results in amentia or idiocy. A similar change setting in during adolescence gives rise at first to manifestations of mental derangement of more irregular and inco-ordinate character before the gradual appearance of dementia signifies obliteration of higher cerebral functions. Later on a similar sequence of premature dotage consecutive to defective development may lead to the insanities of the menopause, and very likely to senile dementia as well. But it is sufficient that we refer only to a few well-marked examples of consecutive senilism of childhood and adolescence.

I. CONSECUTIVE DEGENERATIONS OF CHILDHOOD.

The age of onset, course, and hereditary character of *amaurotic family idiocy* are highly suggestive of premature senile decay setting in in an imperfectly developed cerebral cortex. Children--

* 'Brit. Med. Journ.,' 1878, vol. ii, p. 443.

† Dr. Jacobi, 'Arch. of Pediat.,' vol. xi, 1894, p. 423.

‡ Dr. Tredgold ('Mental Deficiency,' p. 175) says that the muscular helplessness of idiots is often due to agenesis of pyramidal tracts.

almost invariably Jews—affected with this disease are healthy at birth, do well until about six months old, when progressive and general mental decay sets in, and continues until they ultimately die idiotic, blind, emaciated and paretic. After death the brain is found hard and fibrous, the chief change being in the cortex, where the pyramidal cells are destroyed. The neuroglia is increased, and Peterson* describes the nerve-cells in general as being enormously swollen and rounded. He also says that in a case described by him there was some defective development of the cortical cells. Dr. Knapp,† of New York, who first described the disease under the name of “arrested cerebral development,” afterwards re-named it by the title it now bears.

In a case of *Huntingdon's chorea* with dementia recorded by Dr. Robert Jones,‡ a most careful investigation was made in Dr. Mott's laboratory, published by Dr. Bolton.§ In his comments on this case Dr. Jones suggests that it is a presenile condition affecting the higher neurons and is due to some genetic deficiency or hereditary malformation.

Senator,|| in commenting upon a case of *Friedreich's ataxia*, expresses the opinion that the disease is the result of a pre-natal defect of the cerebellum and spinal cord, and that such defective development renders the cord prone to subsequent disease.

Marie expresses the same idea in another way, when he says that he believes that the primary change is a nutritional defect of the ganglion cells.

Friedreich's disease may be *associated* with geneton's idiocy, as in a case recorded by Dr. Nolan,¶ where the combination occurred in three members of a family of eight. There was a family history of tubercle, heart disease and alcoholism, the father being a chronic drunkard. There was no syphilitic taint. Symptoms first appeared in early infancy.

II. CONSECUTIVE DEGENERATIONS OF ADOLESCENCE : DEMENTIA PRECOX.

Drs. Clouston and Skae have described a form of madness setting in between the ages of eighteen and twenty-five, which seems a true precocious dementia.

* ‘Journ. of Nerv. and Ment. Dis.,’ vol. xxv, 1898, p. 529.

† See Dr. Poynton's admirable article, with bibliography, ‘Brit. Med. Journ.,’ 1909, vol. i, p. 1106.

‡ ‘Lancet,’ 1905, vol. ii, p. 1831.

§ ‘Archiv. of Neurol.,’ vol. ii, 1903, p. 603.

|| ‘Berlin. klin. Wochenschr.,’ vol. xxx, 1893, S. 489.

¶ ‘Brit. Med. Journ.,’ 1895, vol. i, p. 815.

This hereditary insanity of adolescence occurs in families which have a profound neurotic taint, is apparently spontaneous in origin, or is started by over-education or by some fever, such as influenza, and is "a sort of premature dotage of the brain." Individuals so affected are promising and healthy up to the time of their attack, but come to maturity sooner than usual. Many of them are industrious or particularly gifted people.

The breakdown occurs, not, as a rule, in those who show defective brain development all round, but where the imperfection is greater in some directions than in others.

Nobody has given more attention to the subject of adolescent madness than Professor Kraepelin of Munich,* who has grouped them together under the name of "Dementia præcox." Dr. Clouston and other alienists have objected to the term "dementia" on the ground that, as applied by Kraepelin, it is too sweeping, and includes not only cases which are not in reality demented, but also some which are recoverable, and, therefore, never will become demented. He prefers the term "adolescent insanity," because those affected often show less of mind decay than of irregularity of mental development, whereby inhibiting influences have not their proper control. Dr. Conolly Norman describes it as an ataxy of the mind, and denies that there is any of that "break-up of the elementary thinking process which occurs in general paresis or in dotage."

Nevertheless there seems to be a pretty widespread consensus of opinion among American and continental alienists that there is a group of insanities of young adults characterised by a process of mental dissolution occurring in those already predisposed, and that the term "dementia præcox" is sufficiently descriptive. Those affected show themselves to be mentally unstable by their exclusive and impulsive ways, by being unduly religious and emotional, eccentric, or too susceptible to the influence of alcohol. Being erratic and unbalanced, their mental ability may be above the ordinary, and they often show the physical stigmata of degeneration. Dr. Stoddart thinks that there is evidence for the view that dementia præcox "should be regarded as a failure in evolution, as an atavism or reversion to the ancestral type."

Kraepelin divides dementia præcox into three ill-defined types, to wit:

* See 'Lectures on Clinical Psychiatry,' by Prof. Kraepelin, revised and edited by Dr. Thos. Johnstone; 'The Mind and its Disorders,' by Dr. W. H. B. Stoddart; and Dr. Macpherson, 'The Review of Neurology and Psychiatry,' vol. v, 1907, p. 185

(1) Katatonic, in which to an accompaniment of stupor or excitement there is marked stereotypism, or the purposeless repetition of the same action; and negativism, or "a senseless resistance against every outward influence." The stupor is often cataleptic.

(2) Paranoid, distinguished by overweening selfishness in an otherwise clear mind, with illusions, hallucinations, or delusions of being wronged or persecuted.

(3) In hebephrenia the more or less rapid mental crises of puberty are the predominating elements leading to uniform mental weakness.

The morbid condition which bears the name of dementia præcox shades off by imperceptible degrees into allied maladies, to which the designation is not suitable. In its typical form it connotes a degeneration of the mind occurring in youths and young adults, who are rendered susceptible by a prior imperfection of the brain, or of some department of the brain.

The Degenerations of the Regressive Periods of Development.

In this sub-group are included tabes dorsalis, general paralysis, lateral sclerosis, disseminated sclerosis, paralysis agitans, syringomyelia, and those combined sclerosis met with in the spinal cord of pernicious anæmia.

Of all these varieties of degeneration we are probably most familiar with tabes and general paralysis, and perhaps the best way of illustrating the general characters of the group is to deal with them first, showing how they tally with the fibrous degenerations of the liver, kidney, and other organs.

TABES DORSALIS AND GENERAL PARALYSIS.

Causation.—In about 90 per cent.* of all cases tabes has been attributed to syphilitic intoxication. According to Ferrier the 10 per cent. in which no history of syphilis occurs can be accounted for on the assumption that the disease is in a latent condition (*S. occulta*). Nevertheless there are other causes. Among them neither age nor sex can be included; for, though the disease

* Dr. Byrom Bramwell states that the occurrence of syphilis could be traced in 59·8 per cent. of his series of 155 cases (*'Brain,'* vol. xxv, 1902, p. 24). Sir William Gowers found syphilis in 68 per cent., probable in 12 per cent., possible in the remaining 20 per cent.

occurs in men of the prime of life, yet, in the words of Dr. Ferrier, "tabes at from thirty to forty years of age is a significant harvest of the wild oats sown some ten years previously, and the classes which sow wild oats most freely are those who reap tabes most abundantly." He then goes on to hint that there are many varieties of wild oats, including excesses of all kinds—alcoholic, sexual, prandial, physical, mental, and religious.

That syphilis alone is not capable of giving rise to tabes is also suggested by the way in which tabes sometimes runs in families. Thus Dr. Nonne* records an instance of its occurrence in a mother and two daughters. One other child, a male, escaped. In such a case the origin of the tabes in childhood, in females, and in three members of a small family can hardly have been due to mere coincidence even though syphilis were present.

It has often been pointed out that syphilis in savage races is not so productive of general paralysis as when it occurs in the civilised, and the punning dictum of Kraft-Ebing that general paralysis is the result of "syphilisation and civilisation" meets with pretty general acceptance. But these are just the causes to which tabes and general paralysis used to be attributed before the overwhelming importance of syphilis became known. We still have to account for the fact that syphilis will give rise to tabes or to dementia paralytica in one individual and not in another, though the circumstances may, to all appearances, be almost identical. It is evident that some factor besides syphilis must be taken into consideration. It has been noticed that the character of the degeneration is often determined by the nature of the stress. Of this fact two good instances are given by Dr. Mott. In one, tabes in a mounted policeman first manifested itself in the arm that held the reins, and in the other, symptoms of amyotrophic sclerosis began in the muscle of the right arm of a cooper. The explanation of this coincidence is that syphilis runs in physiological or paraphysiological grooves. The groove is often prepared by one of the general causes of premature degeneration. Overwork, excessive eating, excessive drinking, privation, may each act as the determining cause of a syphilitic nervous breakdown, and occasionally may be sufficiently strong to bring about the disease by itself, without the aid of syphilis.

So also general paralysis is by some attributed solely to syphilis. Yet it seems almost incredible that those parts of the organism which are of the highest organisation, and are therefore peculiarly susceptible to degeneration, should invariably owe their breakdown

* 'Berlin. klin. Wochenschr.,' Bd. xxxiv, 1897, S. 845.

to syphilis alone. It is far more probable that those* are right who regard the causes of general paralysis as of a complex nature, including syphilis, family predisposition, age, alcohol, and the toxin of influenza or other microbial disease.

The latent tendency to general paralysis may also be brought out by the shock of an injury, or the presence of lead. Lead sometimes "produces a characteristic train of symptoms which may simulate general paralysis in many ways."†

The effect of *pregnancy* upon general paralysis is, according to Gulli,‡ to aggravate the disease. He therefore advises that gestation should never be permitted to go on when these two conditions occur together. He observes that the coincidence is very rare. Probably this rarity is partly to be explained on the ground that dementia paralytica is a parasymphilitic affection, and that sterility or early abortion are therefore of frequent occurrence.

Influence of age.—As is the case with other degenerating influences, the same cause acting upon the brain cortex during the progressive periods of life will tend to produce infantilism and, during the retrogressive periods, senilism. Hence, "there are two types of juvenile general paralysis: (1) Those in which the syphilitic poison seemed to have produced an arrest or impaired development of the higher centres, so that the child was weak-minded or imbecile. (2) Those in which the child was mentally capable, in some cases highly intelligent and active-minded. The cause of the degenerative processes in most of these cases seemed to be associated with the increased psychical activity which must of necessity develop after puberty, when new emotions, objects, and ambitions are awakened by the sexual instinct and the struggle for existence. Alcohol materially increases the rapidity of the progress of the disease."§

Dr. Mott writes that among twenty-two patients with juvenile general paralysis at Claybury the average age was seventeen, and of Thiry's || fifty-eight cases fourteen years.

To sum up, we may say that both tabes and general paralysis are in all probability the outcome of many causes acting together, and by far the most important is syphilis. This, as a rule, is supplemented by overwork, over-excitement, and debauchery of many

* See Drs. Sérieux and Farnarier, 'Revue de Méd.,' 1904, p. 97.

† Dr. Mott, "Investigation of the Causation of Insanity," 'Lancet,' 1906, vol. i, p. 1515.

‡ 'Rassegna d'Obstet. e Ginec.,' June, 1905 ('Brit. Med. Journ.,' "Epitome," December 23rd, 1905).

§ Dr. Mott, 'Brit. Med. Journ.,' 1905, vol. ii.

|| 'Archiv. of Neurol.,' vol. i, 1900, p. 250.

kinds, and by those minor worries and trials of life implied in the word "civilisation," of which the immediate results are the nervous temperament, neurasthenia, the alcohol habit, and sexual immorality. But such an enumeration as this is one of proximal causes only. In regard to the *origin* of these maladies an important factor is yet to come. All these causes are in action daily and in all directions, yet it is only now and again that they give rise to general paralysis. The fact is that, while they constitute the environment which induces, directs, or emphasizes, tabes and general paralysis are, at bottom, fluctuations of development, the origin of which is to be traced to remote biological events.

Rate.—This is very variable. Dr. Byrom Bramwell found that out of thirty-one fatal cases the duration varied from one and a half years to twenty-two years.

Associations.—"Certain *malformations*, or developmental anomalies, such as *heterotopia spinalis*, have been recorded by several observers (Mott, Orr and Rows, Rebizzi) in the spinal cord of those affected by tabes and general paralysis." *

We have already seen that *general paralysis and tabes sometimes occur together*. It has been pointed out that when this happens the general paralysis almost invariably precedes the tabes. Tabes and *progressive muscular atrophy* may also accompany one another. In Dr. Collier's† instance of this association the patient was both syphilitic and addicted to drink. An example of this combination of general paralysis with progressive muscular atrophy is recorded by Dr. Riebnrth.

These same degenerations of the nervous system are frequently associated with degeneration of other organs. One of the most frequent of these associations is that with *chronic Bright's disease*. This subject is gone into by Dr. H. C. Bristowe‡ in a paper read before the Medico-Psychological Society of Dublin. He draws attention to the frequent presence of chronic renal disease in general paralysis, and to the similarity of the changes in the investing fibrous membranes, in the blood-vessels, and in the character of the disease itself in these respective maladies. In discussing the subject he comes to the conclusion that both have a common cause, and believes that this common cause is the arterial sclerosis. We go a step further back, and see that all three—paralysis, Bright's disease, arterial sclerosis—spring from causes which are fundamentally alike.

* Sir Wm. Ferrier, 'Lancet,' 1906, vol. i, p. 903.

† 'Journ. of Nerv. and Ment. Dis.,' vol. xxi, 1894, p. 93.

‡ 'Dublin Med. Journ.,' vol. ci, 1891, p. 446.

Anatomy and Pathology.

It is the opinion of modern neurologists that the disease locomotor ataxia starts in the sensory protoneurons of the spinal cord, and that dementia paralytica begins in the corresponding neurons of the cerebral cortex. Flechsig* has shown that the posterior columns of the spinal cord may be divided into six main divisions, each of which receives its myelin sheath at a different stage of foetal life, and "it is not improbable that tabetic degeneration follows the lines of functionally different fibres," attacking them in the reverse order to that of their development. In fact, the whole "process may be regarded as the inverse of development" (Dr. Mott). Hence the degeneration is selective, keeping to tracts which are of the same functional significance.

Both in tabes and in general paralysis the morbid process does not go direct to the nuclear area of the neuron, but, on the contrary, attacks the cell processes first. "V. Leyden and Goldschieder are inclined to look upon the peripheral nerve-endings as probably the starting-point of the process" (Ferrier).† In brief, there is good reason to look upon the morbid process as a degeneration in the true sense of the word, for it is a retrogressive process, like that which takes place in the nerve-cells of the old man. It is of the same nature as that which goes on in liver-cells in cirrhosis of the liver, and in muscle-cells in progressive muscular dystrophy. There is centripetal and progressive molecular decay, so that the neuron in time becomes worn down to a more or less rounded cell containing but little protoplasm, or at any rate to a cell in which only the nuclear zone is left undamaged.

But a progressive peripheral destruction of neurons must have a corresponding effect upon function, and if the anatomical change resemble that which takes place in normal old age, it necessarily follows that there will also be some correspondence between the symptoms of the degenerative disease and the indications of second childhood. Now we saw, in the first part, that the distinguishing feature of normal senile degeneration is mental retrogression. And this is exactly what happens in general paralysis. The mental attributes of the latest phases of development are the least stable, for they have not had time to become completely fixed by habit. The higher faculties go first, and the others in the order of their

* Sir W. Flechsig, 'Brit. Med. Journ.,' 1906, vol. 1, p. 724.

† "The morbid influence seems to be exerted on the elements of the neuron in greatest degree on the extremities of the fibres, which are the parts furthest from the vital centre." Sir W. Gowers, 'Brit. Med. Journ.,' 1905, vol. i, p. 1.

development. This important generalisation was, as we have already stated, pointed out by Hughlings Jackson in 1868.

A proliferation of the neuroglia network follows closely upon the decay of the myelin sheaths, and of the peripheral axons and dendrons, reminding us of the proliferation of the connective-tissue meshwork of the cirrhotic liver. As in that disease, too, there is a lymphocyte invasion, and the fibroblasts, and perhaps also the lymphocytes, and cells of endothelial origin, after they have finished their phagocytic work on the breaking-down neurons, probably become fixtures in the part, adding to the supply of fibrous tissue.

In general paralysis, likewise, there is dystrophy of the nerve-cells, beginning in their processes, a lymphocytic invasion, the absorption of the outskirts of decayed neurons, and the formation of new fibrous tissue.

Just as the capsule of the liver is thickened in cirrhosis and the walls of the blood-vessels become sclerosed, so also in these nerve degenerations the *pia mater* undergoes thickening with adhesions, and the blood-vessels become implicated in the degeneration.* Sclerosis (endarteritis obliterans) of the local arteries is a common feature of both tabes and dementia paralytica.†

Biological Divisions.

The Developmental Diseases of the Nervous System considered as Variations.

The developmental diseases of the nervous system may be regarded as variations and divided into two series.

The first consists of those which are cryptogenetic or are solely due to heredity, and apparently have nothing to do with environment. It includes :

- (1) Microcephaly and other members of the infantilism group.
- (2) Hereditary spastic spinal paralysis.
- (3) Amaurotic family idiocy.
- (4) Friedreich's disease.
- (5) Hereditary chorea (choreiform diplegia).

The second series consists of those which are partly inherent and partly the result of environment. Among these are :

- (1) General paralysis.
- (2) Tabes dorsalis.

* See Nageotte, 'La Presse Médicale,' No. 99, 1902, p. 1179; No. 1, 1903, p. 5.

† "The Pathology of the Nervous System in Relation to Mental Disease," by Dr. W. F. Robertson, 'Edin. Med. Journ.' 1896, vol. xli, p. 623.

In yet other diseases we cannot as yet say definitely whether they are due to the action of causes, or are idiopathic. Among these are :

(1) Disseminated sclerosis.

(2) Paralysis agitans.

Those of the first group are not only, as a rule, hereditary, but are distinguished by their pronounced character and early onset. They correspond with the discontinuous variations of Bateson, or mutations of de Vries. In this group we must also include most of the defects of development, whether pre-natal or post-natal.

Those of the second group correspond with the continuous variations of Bateson, or fluctuations of de Vries. They vary widely in respect of the part which is played in their causation by internal tendencies on the one hand and by external causes on the other.

Some are largely the result of inborn tendencies ; others are due almost solely to a fitting environment.

The influence of environment is predominant when alcohol, syphilis or debauchery in general gives rise to tabes or general paralysis. But even in such extreme instances as these it is probable that there is always some inherited predisposition.

On the other hand, the influence of inborn characters is sometimes paramount, as when paralysis agitans occurs in brother and sister.* It is said that disseminated sclerosis may also affect more than one member of the same family.† This fact of heredity stamps these particular cases as mutations (major variations).

Then there are many other less defined mental diseases which are of spontaneous origin and hereditary. "Parents who have suffered from hallucinatory insanity with fixed delusions—cases of paranoia—often have children who grow up "cranks," "eccentrics," "oddities," etc., and they appear to transmit the character which they themselves possess" (Dr. Robert Jones).

We must also include in the same category certain exceptional cases in which a non-hereditary disease occurs at an unusually early age. Thus an instance is recorded‡ of a lad of eighteen of strikingly juvenile appearance, "similar to that of a child of twelve," who was affected with paralysis agitans.

* 'Lancet,' 1902, vol. i, p. 1097.

† Stieglitz, 'Amer. Journ. Med. Sci.,' 1898, vol. cxv, p. 159. Dreschfeld's hereditary cases ('Med. Times and Gaz.,' 1878, vol. i, p. 140) were in two brothers of seven and nine; Totzké's ('Dissertation,' Berlin, 1893) in two sisters of eleven and fourteen.

‡ Dr. Lannois, 'Lyon Médicale,' 1894, No. 14, p. 465.

VII

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF THE GASTRO-INTESTINAL TRACT

Overgrowth is met with as a rule in infancy, and is especially apt to be localised in the pylorus. **Defective development** is also met with. As a rule, the disorder which occurs most often is **degenerative hyperplasia**. This accounts for many cases of pyloric enlargement, and in all probability for most cases of cancer, the cancerous degeneration being secondary.

Introduction.

THE diseases now under consideration are greatly modified by the natural peculiarities of normal stomach structure. When we compare the stomach with such an organ as the liver or kidney, we see that it differs in two important particulars. It is not a compact, solid mass of conglomerated tubes, but resembles the skin in consisting of a sheet of glands laid upon a substratum of fibrous tissue. The analogy is the more evident when we remember that in certain parts of the body the skin contains a muscular layer which corresponds in situation with that of the muscular coat of the stomach. Hence, though it is true that the one organ proceeds from the hypoblast and the other from the epiblast, and that in the one the muscles are striated and in the other are not, yet there is such a correspondence between them as must needs bring their affections of growth and development into proximity.

In certain parts of the surface of the body the functions of the tissues are more pronounced, and tend to gather themselves together into more or less special organs, such as the hands and the feet and the face. So also is it with the stomach. In this organ, too, there is no even distribution of function; for while the parts about the cardiac end have the more passive uses of a mere receptacle, as we approach the pyloric end the more active muscular parts of the organ come into play, and these reach their climax at the pylorus itself, which forms almost as definite an organ at the end of the stomach as the hands and feet do at the extremities of the limbs.

Just as on the surface of the body developmental disease is most likely to affect those parts in which function is most specialised, so is it with the organ we are now considering. Although the stomach as a whole may be affected with overgrowth or with degeneration, we shall find this process occurs most often and in most marked form at the pylorus.

It has furthermore been noticed that an anomaly of growth or development is most apt to appear at those times of life when function undergoes its most marked changes. Now the stomach passes through its most rapid changes of form and performance during early infancy, when it is first coming into use. This, therefore, is the most likely time for overgrowth, as well as for the degenerations which arise out of them. Normal retrogressive changes, on the other hand, are spread over the latter half of life, and premature degeneration, or fibrosis, is therefore less limited as to the time of its appearance.

A. Undergrowth and Overgrowth of the Stomach.

There can be but very little doubt that the stomach is sometimes too small without being undeveloped, and too large without being over-developed or prematurely old. Moreover, there is reason to believe that the overgrown organ, or its pylorus, may either resume its proper size or may pass on into degenerative hyperplasia. Further discussion of this subject of pyloric overgrowth will be left until we come to that of the degenerative enlargements.

B. Defective Development or Infantilism of the Stomach.

Stomachs of an unusually small size are sometimes found after death, generally in association with some other defect of growth or development, especially of the alimentary canal. Such a case is described by Dr. P. F. Barbour* as occurring in a girl of eighteen, who had suffered from persistent vomiting for many years. The stomach would not hold 4 oz. (112 c.c). Though it was not occluded, the upper 3 in. (7.5 cm.) of the duodenum was thickened by a hard fibrous mass constricting the tube. There was also a pre-natal stricture at the junction of the rectum with the sigmoid flexure, and the ovaries and uterus were of defective size.

As a rule the stomach with a contracted pylorus is dilated, but sometimes stenosis and contraction go together. When this happens

* 'Arch. of Pediat.,' vol. xiii, 1896, p. 275.

it is probable that the stomach is of defective development in the first place, and that the degeneration of the pylorus is secondary. Thus an instance is recorded* of a man, aged 46 years, who was found to have a stomach so small that it would hold only 60 c.c. of fluid. Its walls were everywhere thick, so that they measured 1.5 cm. ($\frac{3}{5}$ in.) towards the pylorus and 1 cm. ($\frac{2}{5}$ in.) at the greater curvature. This thickness extended to the duodenum and included the exit of the common bile-duct. The thickness was mainly of the muscular coat, but mingled among its fibres were many bundles of new connective tissue. The condition, in short, was one of degenerative hyperplasia. The patient was a free drinker, but in all probability the alcohol was not alone responsible for the degeneration. The extremely small size of the stomach suggests that it was originally of defective development, and that this infantilism greatly facilitated the action of the alcohol. In other words, it is most likely that the senilism was preceded by infantilism.

C. Premature Senile Degeneration or Senilism of the Stomach.

I. *Degenerative Hyperplasia.*

Instances have been reported in which the whole of the stomach has been affected with an almost uniform enlargement. The thickening of its walls may then be so evenly distributed and extreme that it retains its shape when empty, although there is no definite constriction of the pylorus.† But in most cases the part chiefly affected is that which lies towards the pyloric end, giving rise to the funnel-shaped stomach described by Dr. Praeger‡ In this kind of stomachs the thickening increases as the pylorus is approached, and, having reached that part, ceases abruptly. A remarkable example of this deformity, given by Dr. Maylard,§ will be referred to later on (pp. 340-1).

In spite of their dissimilarity there seems to be no essential difference between those enlargements of the pylorus which are met with in children and those which occur in adults. The differences can be accounted for on the grounds of age alone, the enlargement in adults being more fibrous and those in infants more muscular and hyperplastic.

* Drs. Marcy and Crozier Griffith, 'Amer. Journ. Med. Sci.,' vol. lxxxviii, 1884, p. 182.

† As in Dr. Pitt's case, 'Path. Soc. Trans., Lond.,' vol. xliii, 1892, p. 63.

‡ 'Virchow's Archiv,' 1885, Bd. cii, Heft 3, S. 28.

§ 'Lancet,' 1904, vol. ii, p. 1709.

The first important publication on the subject of the ante-natal form seems to have been the thesis of Landerer.*

Thirty cases recorded by Maier† in 1885 were mainly adult, though some were in children of over ten years. Tilger's exhaustive article on the same subject‡ was also chiefly concerned with adult cases; but since Hirschsprung's paper, written in 1888,§ giving a full account of the pre-natal and infantile forms, attention seems to have been directed mainly to this early variety.

Surgeons experienced in abdominal operations are acquainted with a non-malignant overgrowth, or degenerative hyperplasia of the pylorus. A patient so affected presents all the aspects of cancer of the pylorus, and the surgeon before whom he is brought is usually pleased to find that despite the large size of the tumour, the dilated condition of the stomach and the thinness of the patient, there are as yet no adhesions. He therefore operates, and, finding an uniformly large smooth swelling of the pylorus, either cuts it out or connects the stomach with the duodenum or jejunum. In the former event a microscopic examination of the growth fails to reveal the presence of cancer-cells, and nothing is visible but a large excess of fibrous tissue with much cell infiltration. If the short-circuiting operation be done the innocence of the growth is proved by its subsequent disappearance.

We ourselves have had experience of such a case. The patient, a woman, aged 52 years, was almost at death's door from starvation when we first saw her. Thinking the disease to be cancerous, a preliminary gastro-duodenostomy was advised, to be followed by pylorotomy if the conditions were favourable. This first operation was carried out under a local anæsthetic assisted by a few whiffs of chloroform. The growth was found to be so smooth and uniform and so completely confined to the pylorus that no serious difficulties were apprehended when the time came for removing it. The patient speedily improved in weight and strength as the result of the first operation, and, in an unfortunate desire for a radical cure, we embarked upon the second operation for the removal of the supposed cancer. But though the first incision had healed without the slightest disturbance, and without so much as a twinge of pain, and though no more than three weeks had gone by since the operation, the stomach was already so bound down with adhesions that the relations of the parts were hopelessly obscured. The pyloric growth was undoubtedly smaller. No attempt was

* "Ueber angeborene Stenose des Pylorus," Inaug. Diss., Tuebingen, 1879.

† "Beiträge zur angeborenen Pylorus Stenose," 'Virchow's Archiv,' Bd. cii, 1885, p. 413.

‡ 'Virchow's Archiv,' Bd. cxxxii, 1893, p. 290.

§ 'Jahrb. für Kinderheilk.,' Bd. xxviii, 1888, p. 61.

therefore made to remove it, and the wound was sewn up. But notwithstanding that the second operation was so much slighter than the first, and though no convincing signs of septic infection appeared, vomiting started immediately after the operation, and continued until the patient died five days afterwards. Subsequently, on examining the pylorus, no sign of cancer could be detected. There was almost uniform fibrous hyperplasia of the submucous and muscular coats. No secondary growths could be found in the lymph-glands, or liver or elsewhere.

Clinical Characters.

Causation.—Those enlargements of the pylorus which occur in infancy have been attributed to spasmodic action of the sphincter muscle set up by the swallowing of liquor amnii during foetal life. But it is not easy to accept this view. The disease often does not make its appearance until some weeks or months after birth, and the microscopical character of the swelling in many cases gives very little support to the theory that the derangement is ultimately of a functional character, though it may have begun as a simple overgrowth.

But though there is no satisfactory evidence that hyperplasia of the stomach or pylorus of early life has any adequate causation, the widespread fibrotic degeneration of after life has many causes. Chief among these are *alcohol*, excessive or unsuitable food, and *gout*. These act upon the stomach much as they do upon the liver or kidneys when they set up corresponding degeneration of those organs. As a rule there is first gastritis, just as there is hepatitis or nephritis, and this inflammation, when often repeated, acts both as cause and consequence of the retrogressive development and premature senile decay.

Heredity.—Degenerative hyperplasia is rarely inherited. Dr. Ashby says that it may occur in two or more members of the same family.*

Age.—The hyperplasia is by some regarded as ante-natal in origin, but usually the symptoms (and probably the disease) first appear in the second or third week, though they may be delayed for a month or two months (Dr. Gardener). In Dr. Maylard's case the hyperplasia began at twenty.

Prognosis and treatment.—In a series of cases published by Dr. Still,† nine out of twenty required operation (forcible dilatation),

* 'Arch. of Pediat.,' vol. xiv, 1897, p. 498.

† 'Lancet,' 1905, vol. i, p. 632.

and seven ultimately recovered. Recovery often ensues after lavage and careful feeding.* In a patient of Dr. Batten's† recovery took place, though the case was a severe one, but subsequently the child died from diarrhœa and vomiting, and after death the whole stomach was found thickened, especially in its muscular coat. This thickness was most pronounced at the pylorus. Considerable improvement had evidently taken place since the beginning of the disease. The spontaneous disappearance of the tumour, which sometimes occurs, reminds one of the disappearance of the hyperplasia in scleroderma and of muscle in pseudo-hypertrophic paralysis.

Mr. Clinton Dent advises that the operation of pyloroplasty should be carried out in preference to dilatation, and Dr. Cautley ('Diseases of Children') is of the same opinion.

Associations.

For physiological reasons the diseases of development which most often appear in conjunction with the degenerations of the stomach are those of other parts of the gastro-intestinal tract, and these diseases are then either defects of development or are themselves degenerations. The latter occur for the most part during the retrogressive years of development, and the defects of development are, of course, usually found during the progressive periods.

Pre-natal stenosis of the pylorus is prone to be associated with other pre-natal anomalies, such as *hour-glass contraction*‡ and occlusion of the duodenum.§

Dr. Cautley,|| in a paper on "Congenital Hypertrophic Stenosis of the Pylorus," describes a case in which there was also a large cavity in the right hemisphere of the brain.

In Dr. Maylard's case¶ of funnel-shaped stomach, due to hyperplastic stenosis of the pylorus and of the pyloric third of the stomach, there was also increase of *fibrous* tissue in the portal area of the *liver* and chronic *fibrosis of the kidneys, spleen, and pancreas*.

Another important association is that of *pernicious anæmia*, which will be referred to in the chapter on the diseases of the blood-forming organs (p. 399).

* Dr. Blaxsland, 'Lancet,' 1905, vol. ii, p. 826.

† *Ibid.*, 1899, vol. ii, p. 1511.

‡ As in one of Dr. John Thomson's cases, 'Edinburgh Hospital Reports,' 1892, p. 116, and in Dr. Turner's case, 'Path. Soc. Trans., Lond.,' vol. xxxviii, p. 139.

§ Dr. Ashby, 'Diseases of Children,' p. 158.

|| 'Med.-Chir. Trans.,' 1899, S. 2, vol. lxiv, p. 41

¶ 'Lancet,' 1904, vol. ii, p. 1709.

Anatomy of the Hyperplasias of the Stomach.

Enlargements of the pylorus are generally described as "hypertrophies," but when details of structure are gone into, the increase has usually proved to be, not functional, but degenerative in character. It is true that in some cases the muscle alone is involved. Thus in the three cases described by Dr. Still* the enlargement was said to be entirely muscular and to affect chiefly the circular layer, and this may also be said of Dr. Thomson's case† which he stated to be one of "pure muscular hypertrophy." It is evident, therefore, that in some instances a true muscular overgrowth is met with, but most appear to come under the denomination of degenerative hyperplasia. And even when the muscle only is affected there may be evidence that the overgrowth is associated with a certain amount of degeneration. Thus, in Dr. Maylard's case, in which nothing but muscle seemed to be implicated, a careful microscopical examination showed areas of new fibrous tissue between the muscle-bundles. Moreover, in other parts of the stomach, the submucous coat was found to be thickened and the mucous coat atrophied, so that there was loss of glandular substance.

Dr. Cyril Ogle‡ has described a fibrous stricture, similar to Dr. Maylard's case, also occurring in an adult. The pyloric half was alone affected. The walls were, on an average, half an inch thick, but were decidedly thicker towards the pylorus. Microscopic examination showed no evidences of cancer, but the muscles and submucous coat were greatly thickened and the mucous membrane was thrown into folds.

In Schwyzer's patient§ the section showed "mucosa greatly, muscularis enormously, serosa somewhat thickened, and marked mucous degeneration in the glandular epithelium, between which and the subepithelial tissue are leucocytes." A large number of connective-tissue cells were also found among the fibres of the muscularis mucosa.

Even when the microscope has been used, and the muscle is said to be simply hypertrophied, it is sometimes evident, from the description, that a different meaning is given to the word "hypertrophy" than is consistent with accuracy. Thus, in Mr. Peden's case|| the muscular fibres were first said to show "marked hypertrophy," and

* 'Path. Soc. Trans., Lond.,' vol. 1, 1899, p. 86.

† 'Edinburgh Hospital Reports,' 1892, p. 116.

‡ 'Path. Soc. Trans., Lond.,' vol. xlv, 1895, p. 56.

§ 'New York Med. Journ.,' vol. lxvi, 1897, p. 726.

|| 'Glasgow Med. Journ.,' vol. xxxi, 1889, p. 416.

were then described as of a reticulated aspect due to "enormous hypertrophy of each individual muscle, all giving the appearance, roughly speaking, of a large nerve-fibre, seen on cross-section—the nucleus was central and enlarged, the periphery of each muscle-cell had a large, coarse, fibre-like outline." It was this outline, when pressed together into a hexagonal shape, which gave the reticulated appearance to which he refers. It is evident that such an appearance is abnormal and degenerative in character. In fact, Mr. Peden afterwards referred to the stenosis as a "malformation" and agreed with Dr. Adams that it was "a vice of developmental growth."

It is difficult to find two cases alike. They vary indefinitely. Though as a rule the enlargement is, in the main, of the circular fibres of the pylorns, sometimes it is the longitudinal which are most affected. In some the muscle escapes and the thickening is chiefly of the submucous coat or of the subserous; in others it is almost confined to the mucous membrane and submucous tissue, so that they are thrown into folds or become polypoid.

We may, indeed, say of the stomach what we have already said of the giant hand, of the cirrhotic liver, and of the kidney of Bright's disease, that the disease may begin and remain preponderant, in any part; it may diffuse itself irregularly over the different structures of the organ, or may be disseminated in the form of patches. In short there is as much diversity in the structure of the fibroses of the stomach as there is of any of the diseases which we have just mentioned.

II. *Senilism of Hypoplastic Type.*

Professor Nothnagel* describes three chief forms of atrophic degeneration of the stomach. In one there is complete disappearance of the glands with or without fibrosis. In the second the whole thickness of the stomach atrophies, in extreme cases the walls becoming as thin and transparent as oiled paper. In the third there is atrophy of the glands, consecutive to chronic gastric catarrh, the fibrous tissue increasing in quantity and destroying the glands by its contraction. Cysts may be formed, as in fibrosis of the kidney. The disease is incurable and the prognosis consequently grave.

In this *atrophic form* of degeneration the mucosa and submucosa may, in extreme cases, almost disappear (Nothnagel), so that hardly anything but a diaphanous semi-transparent layer of fibrous tissue, with a few muscle-fibres, is left.

* 'Allgem. Wien. med. Zeitschr.,' Bd. xxiv, S. 91.

In a case of this kind, detailed by Dr. Brabazon,* the stomach is described as being like brown paper soaked with water. The atrophy of muscular and fibrous coats was so extreme that a ligature placed round the œsophageal opening cut through it as if it had been wet blotting-paper. The patient was a lady of sixty-three, in whom no cause could be found for the condition, though she was suffering from extreme anæmia. No examination of the blood was made.

Degeneration of the Intestines.

Just as we have spontaneous enlargement with degeneration of the stomach, so may we have spontaneous degenerate overgrowth of other parts of the intestinal tract; and this, too, is most prone to occur in those parts of the intestines in which there is most segregation of structure and function. One of the most striking instances is degenerative hyperplasia, or "giant growth of the colon" (Virchow), which gives rise to such enormous distension of the abdomen that men so affected have exhibited themselves to the public as "balloon men," as in Formad's celebrated case. It is characterised by dilation of the abdomen of peculiar shape, and by periods of obstinate constipation, alternating with diarrhœa. The only treatment is by operation, an artificial anus being made in the right iliac region; or, still better, the lower part of the ileum may be diverted into the end of the descending colon. This operation was first performed by Sir F. Treves with excellent results.†

Relations with Cancer.

It has been noticed that cirrhosis of the liver may pave the way for diffuse carcinomatosis, and that the cancer is then, as a rule, of local malignancy only. Possibly the gall-bladder, too, may undergo diffuse carcinomatosis of similar degree of malignancy if we may so interpret the case given on p. 170. Moreover, the diffusion of the cancer, its uniformity, and its markedly fibrous character suggest that it starts in a general fibrous degeneration. The stomach is yet another organ in which there is apparently a very close connection between the diffuse degeneration of the organ and the local cell-degeneration we term "cancer."

So often, in fact, does local carcinomatosis occur that Dr. Fagge‡

* 'Brit. Med. Journ.,' 1878, vol ii, p. 134.

† From 'The Principles and Practice of Medicine,' by Professor Osler, 6th ed., p. 532.

‡ 'The Principles and Practice of Medicine,' ed. 1, vol. ii, p. 146.

has stated that all cases of marked hyperplasia of the stomach and pylorus are in reality carcinomatous, the absence of secondary growths being due to the fact that life is destroyed before they can be formed. This statement of Dr. Fagge's is borne out by investigations of Drs. Perry and Shaw,* who, as the result of an examination of fifty cases of malignant disease of the stomach, came to the conclusion that chronic cirrhosis of the stomach is invariably malignant, except when due to traumatism.†

On the other hand, well-attested cases of non-cancerous fibrosis have been brought forward. We must particularly mention Dr. Ogle's case of fibrous hyperplasia affecting the pyloric half of the stomach, because he especially drew attention to this fact of non-malignancy in view of what Dr. Fagge had said.

Fibrous degeneration of the stomach so often merges into diffuse malignancy that, without microscopical examination, it is, as a rule, impossible to say whether we have to do with the one disease or the other. This difficulty occurs because, as was stated in the chapter on cancer, diffuse carcinomatosis and fibrosis tend to approach each other, not only structurally, but in their symptoms and prognosis. When cancer is confined to the organ and is widespread, and does not diffuse itself metastatically, it runs an insidious, chronic course, and may have all the appearances of being no more than a fibrosis. But there is a different state of affairs when the cancer is not diffused, but starts in a confined area. It then shows its characteristic features, and, generally speaking, the more circumscribed it is the more characteristic is its course, its dissemination, and its symptoms.

Ring cancer of rectum.—There is one other part of the gastrointestinal tract in which the single cell degeneration of cancer, by being diffused, merges into the milder degeneration peculiar to organs. This intermediate kind of degeneration occurs in the rectum. So-called fibrous strictures of the rectum are sometimes occasioned by a ring of thick, hard, fibrous tissue, completely surrounding the bowel. Some of these may be in truth no more than fibrous hyperplasia of the organ, but others are in reality cancers, probably arising out of the former. The cancer is then only locally malignant, giving rise to mechanical effects only, not ulcerating until it has been in existence a long while, and presenting no secondary phenomena. It is very different from the usual cancer of the

* 'Guy's Hospital Reports,' vol. xxxiii, S. 3, 1891, p. 137.

† See also Dr. Handford, "Diffuse Sarcoma of the Stomach," 'Path. Soc. Trans., Lond.,' vol. xl, 1889, p. 89.

rectum, which arises at one spot, or, at any rate, is far less diffuse in its origin, and runs the usual cancer course.

We have recently seen two well-marked cases of the locally malignant kind of rectal cancer.

One we first saw five years ago in an old lady of seventy-eight years of age, in whom symptoms (chiefly spurious diarrhœa) had been in existence and gradually increasing for more than three years. The central orifice, or lumen of the contracted tube, would then just admit of the insertion of the tip of the little finger. We advised that no operation should be done, and the lady is still alive and well, and shows no signs of metastasis. No microscopic examination has been made, so that the diagnosis is clinical only. The growth has ulcerated so that liquefaction of fæces and frequency of defæcation are not so troublesome.

In another case, that of a woman of thirty-eight, as the aperture was so small as to give rise to definite obstruction, a cut was made and a slice removed for examination. The stricture was then well dilated. The growth was found to be a fibrous, spheroidal-celled carcinoma. Though the operation was done nearly six years ago there has been no sign of the growth spreading. The lady uses a dilator daily.

VIII

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF THE ARTERIAL SYSTEM

All forms of disorder of growth and development are met with, the most important being **overgrowth** (hypermyotrophy) and **degenerative hyperplasia** and **sclerosis**. But **defective development** is also of much consequence, seeing that in all probability it often precedes and paves the way for sclerosis. The *causes* of the degenerative disorders are such as account for senility and pre-senility of other organs, and are usually of the internal or toxic order. Either one, or two, or all three of the coats of the artery may be implicated.

Classification.

THOUGH undergrowth of the arterial system has not yet been separated from under-development, true functional overgrowth (hypermyotrophy) is gradually being recognised as distinct from degeneration.

Defective development is well defined from degeneration, and the latter is capable of further division.

Hence we have, academically, the following classification :

I. *Growth.*

- (1) Undergrowth, or hypoplasia.
- (2) Overgrowth, or hyperplasia.

II. *Development.*

- (1) Defective development, or infantilism.
- (2) Premature senile decay, or senilism.
 - (a) Degenerative hyperplasia, or arteritis deformans.
 - (b) Degeneration, or sclerosis.

Subdivisions founded upon site (inner, middle, external coats), locality (brain, abdomen, kidney, heart, uterus, etc.), age (juvenile, adult, senile forms), will subsequently be referred to.

Overgrowth.

It was at one time believed that the thickening of the middle coat in hypermyotrophy was a physiological change and due to

excessive action of the muscle in the pursuit of its normal function. This idea was carried to its logical conclusion by Dr. George Johnson when he started his "stop-cock" hypothesis. He pointed out that the blood in chronic Bright's disease is probably poisoned by the products of metabolism, which are retained in the body instead of being cast out through the kidneys. To save the tissues from being damaged by this vitiated blood the arterioles contract and partially cut off the supply. Then the heart hypertrophies in order to propel an adequate supply of blood through the obstruction, and so the vicious circle is completed.

There is reason to believe that overgrowth of one or more arterial coats may, indeed, come into existence, not only as the result of uræmia, but of gout, alcohol, or other toxin. At any rate, there is such a condition as arterial thickening with or without hypertonus, which completely disappears in response to treatment, and in other ways behaves rather after the fashion of a less permanent overgrowth than of a more permanent degeneration.

Hypermyotrophy, it must be remembered, extends laterally as well as vertically, so that the artery is lengthened as well as thickened, and in order to accommodate itself to its surroundings becomes sinuous. These changes are well shown in the temporal artery. Not only does this artery stand out conspicuously by reason of its increased thickness, but it is obliged to run a tortuous or cork-screw course because of its inordinate length. Now it is conceivable that the muscular coat of an artery may increase in thickness because of some extra call upon its function, but it is less easy to suppose that there can be any advantage in the vessel becoming double its usual length. It seems much more likely that the change is either a morbid overgrowth or is a presenile phenomenon, coming either spontaneously, as the result of variation, or induced by some of those causes which are known to favour the onset of old age. In the latter event it corresponds with that enlargement of the uterus which sometimes precedes the menopause, presently to be referred to, and with the thickened, lengthened, and weakened tibia of osteitis deformans.

In some cases of thickening of the middle coat no increase of fibrous tissue can be detected, nor is there any excess of embryonic cells, yet the individual fibres look far too big. This last change is, of course, highly suggestive of degeneration, but Dr. Saville* says that he has repeatedly seen similar appearances in normal arteries taken from perfectly healthy subjects. It is, therefore, in this case

* 'Lancet,' 1904, vol. ii, p. 879.

not a good test of deterioration, but may be the result of simple hyperplasia. He also says that "true degeneration is revealed by granular (and perhaps cloudy) or other changes in texture."

Defective Growth and Defective Development, or Infantilism.

Defective development, or hypoplasia, of the heart and arteries was believed by Virchow to be the chief cause of chlorosis. But we now know that cardiac hypoplasia is common to both sexes. It therefore seems improbable that it should be the main cause of chlorosis, which is almost exclusively a feminine derangement. At the same time, Virchow was far too acute an observer to have been altogether mistaken. More will therefore be said on this subject when we come to that of chlorosis.

Dr. Paradis,* as the result of careful investigation, says that in some cases of arterial hypoplasia, making itself manifest at puberty, the disease originates before birth, and is, therefore, in reality a pre-natal error of development. Dr. Paradis alludes to the sexual defect which sometimes accompanies the arterial hypoplasia, and states that it is one of the causes of general infantilism. It is, indeed, supposed to be the chief factor in the production of the Lorain type of general infantilism, and will, therefore, be referred to again under the heading of general infantilism (p. 568).

We should expect that those who have imperfectly developed arteries would not only, if females, be liable to chlorosis, or to be of somewhat stunted growth or defective development, but would also be prone to die prematurely from apoplexy, heart disease, or some other consequence of arterial sclerosis. It is, indeed, highly probable that infantilism of the arteries accounts for all cases of juvenile arterial sclerosis.

Premature Senile Decay or Senilism of the Arterial System ; Varieties.

Degeneration of the arteries occurs in two chief forms. In the one the change is mainly in the direction of hyperplasia ; in the other it is almost purely fibrous and hypoplastic.

Degenerative hyperplasia.—Degeneration is sometimes so intimately associated with overgrowth (hypermyotrophy) that it is difficult to separate them, functional overgrowth shading off by imperceptible degrees into degenerative hyperplasia. This latter,

* 'Thèse de Lyon,' 1902 ; 'Brit. Med. Journ.,' "Epitome," 1903, vol. ii, p. 9.

as a rule, is a disease of the middle coat, and may give rise to so much disfigurement of the vessel as to warrant the name of *arteritis deformans*. It may even block the lumen of the artery, and is then termed *obliterative arteritis* (Friedländer). Arterial tissue affected with degenerative hyperplasia gradually wastes, so that, like the thickened skin of scleroderma and the thickened muscle of muscular dystrophy, the hyperplastic often ends in the next, or atrophic form.

Fibrous or hypoplastic degeneration.—Any one of the three coats of the artery may be the starting-point of degeneration, or two or three may be affected together, though in different degrees. Dr. Saville,* therefore, divides arterial sclerosis into three chief forms—the intimal, the medial, and the adventitial.

Arterial sclerosis (as well as degenerative hyperplasia) may also be classified according to the particular part of the arterial tract involved. Though the disease is usually diffuse it may be *partial* or *nodose*, and as a primary disease affect mainly the *cerebral*, the *abdominal*, the *renal*, the *uterine* or the *cardiac* (Stengel) area, or it may be confined to some other system. The “*diffuse* arterial sclerosis” of Mott begins in the small arteries and capillaries, especially of the kidneys, brain, or heart, and from thence spreads to the whole arterial system.

Arterial sclerosis may also occur as part and parcel of some local degeneration, as in the giant hand, cirrhotic liver, small red kidney, degenerating uterus, and never extend beyond the area in which it begins. It occurs in pronounced form in the involuting puerperal uterus.

Arterial sclerosis, moreover, is sometimes the starting-point of degeneration in other organs. Thus, we have already noticed it as the beginning of some cases of cirrhosis of the liver and of granular kidney. Probably there is no organ degeneration in which it may not be the initial change, so that arterial degeneration forms a connecting bond between all the local varieties of senilism.

In brief, it is evident that the same may be said in effect of the degeneration of arteries as of the degeneration of other organs. It may begin in any structure which enters into the composition of the vascular system, and give rise to a corresponding variety. In other words, the extent of variation which the disease may assume is only limited by the bounds of the normal structure and function of the part affected.

* ‘Lancet,’ 1904, vol. ii, p. 879.

Ætiology.

The causes of arterial degeneration are in every way similar to those which bring about degeneration in other organs. Arterial degeneration is due to the action of *lead*, *syphilis*, *gout*, or to the *toxin* of some infective fever, such as enteric fever (Thayer), diphtheria, smallpox, or pneumonia.

Perhaps none can speak with greater authority upon this subject than the doctors who practise at German spas. Their experience, as expressed at a meeting of the Balneological Society, Berlin, in 1905,* coincides with that of other physicians in respect to the importance of the causes just named. They were, moreover, of the opinion that muscular *exertion*, even if prolonged and excessive, is not *per se* a causative factor, though it may be so when it acts in conjunction with toxins. Dr. Edgren† states that *chronic alcoholism* accounts for 25 per cent. of cases of arterial sclerosis, and Professor Sims Woodhead,‡ as well as Sir Victor Horsley,§ also believe that alcohol, not necessarily taken in excess, but if habitually taken in small doses, is a cause of arterial sclerosis.

On the other hand, Dr. Barr || denies that *alcohol* ever acts as a cause, and says that Cabot, Lancereaux, and Duclos are of the same opinion.

How difficult this problem of causation may be is shown by an inspection of Dr. Huchard's figures.¶ He found that alcohol accounted for only 52 out of 2680 cases of arterial sclerosis, yet *gout* and *lithiasis*, which are so largely the result of alcohol, were responsible for 693.

Moreover, influences are regarded as causes which are in reality effects or only coincidences. Thus, not only gout, but rheumatism and diabetes, which are usually regarded as causal, may sometimes be mere associations of arterial degeneration.

Syphilis is said by Edgerton to be a very important factor. He believes that no less than one case in every five is produced by syphilis. Huchard says one in eight.

Probably of as much importance as any other cause is the *excessive*

* Dr. Manfred Fraenkel, 'Wiener klin. Rundschau,' 1905, Nos. 29 and 30.

† 'Die Arterio-Sclerosen,' Leipzig, 1898, from 'The Nature of Man,' p. 247, by Professor Metchnikoff.

‡ 'Practitioner,' vol. lxi, 1902, p. 539.

§ 'Alcohol and the Human Body,' 2nd ed., p. 272, with Dr. Mary D. Sturge.

|| 'Brit. Med. Journ.,' 1906, vol. i, p. 121.

¶ "Internat. Med. Congress at Budapest, 1909," from 'Le Monde Médical,' October, 1909.

use of *nitrogenous foods*, especially those which occur in meat. Huchard regards "alimentary habits" as almost equal to syphilis as a cause.

Dr. Stengel* believes that continual *mental anxiety* is of some ætiological importance, especially if combined with alcoholic intemperance, and Huchard lays stress upon *moral and intellectual overstrain*, which he believes act by means of the vascular spasm to which those who live lives of emotion and high nerve-tension are so peculiarly liable.

Tobacco comes fifth in order in Dr. Huchard's statistics. Dr. Huchard invokes the evidence of Claude Bernard's experiments, demonstrating the vaso-constrictor action of nicotine, as well as those of Adler and Hensel (1906), and of still more recent observations. Nevertheless, tobacco can only be attributed as a cause in one fourteenth of his cases, and when we think of the extent to which tobacco is used and abused, its potency can hardly be very conspicuous.

Dr. Emerson Lee, who has experimented on the "action of tobacco smoking, with special references to arterial pressure and degeneration,"† found that nicotine is the injurious agent, and that the pyridin bases are harmless. Smoking first raises blood-pressure by vaso-constriction, and then lowers it by depressing the vaso-motor centre. He came to the conclusion that the prolonged action of tobacco is capable of giving rise to arterial sclerosis in rabbits. Similar, but more decisive, results have been produced by the injection of *adrenalin*. These experiments seem to indicate that anything which produces prolonged or repeated rise of blood-pressure is capable of setting up fibrous degeneration of the arteries. At any rate, Harvey‡ and Klotz,§ working independently, came to the conclusion that adrenalin fibrosis is produced in this way, and not by means of any other intoxicating effect.

In all probability arterial sclerosis can rarely be attributed to one cause alone, but is due to the action of two or more acting together, and it must necessarily be very difficult exactly to compute the effects of each component of the mixture.

Age must, however, be regarded as the chief factor in the production of arterial fibrosis, for the disease is far more common after middle age than before.

* Nothnagel's 'System.' Dr. Mott (Allbutt and Rolleston's 'System of Medicine,' vol. vi, p. 585) says that pregnancy appears to favour the appearance of arterial sclerosis.

† 'Quarterly Journal of Experimental Physiology,' vol. i, 1908, p. 335.

‡ 'Journ. Exper. Med. N.Y.,' 1906, vol. viii.

§ *Ibid.*, 1905 and 1906, vols. vii and viii.

This is, of course, in great part due to the fact that the above causes have had opportunity of coming into play. But there is also reason to suppose that there is some other circumstance to be taken into consideration. Drs. Key and Aberg* found, after careful statistical researches, that liability to the disease does not increase as age advances, for in most cases arterial degeneration occurs between forty and forty-four, that is, at the beginning of the retrogressive periods of life. It is at this time, or a little later, that we meet with degenerative hyperplasia of the uterus. We have already seen that there is a strong tendency for *defects* of development of the vascular system to be associated with defects of development of the genital organs; and it fits in with all that we know of the relations of developmental diseases that *degeneration* of the arteries and of the sexual organs should also occur together at about the same period of declining development.

Sometimes degeneration begins still earlier, so that occasionally men under thirty die from thrombosis of the cerebral arteries, consecutive to sclerosis. A *juvenile form* is recognised by some writers. Probably the earliest age on record was that of a child under Drs. Bryant and Hale White. This patient was only six months old at death, and was affected with obliterative endarteritis with calcification, giving rise to gangrene of the right foot. The disease was of irregular distribution and was associated with hydronephrosis, thought to be of pre-natal origin. In all probability the degeneration in these early cases is secondary to a prior defect of arterial development.

Heredity.

Not infrequently early degeneration of the arteries occurs independent of any definite cause. It is one of the well-known axioms of life assurance that if both parents of a man died from "apoplexy" at an unusually early age, the life prospects of the son are seriously handicapped. No matter how carefully he may order his ways, it is not likely that he will live many years beyond the age at which they died. It is a matter of common knowledge that a tendency to early arterial sclerosis exists in some families.†

Anatomy and Pathology.

In dealing with the degeneration of the arterial system it is very important that atheroma should not be confused with degenerative

* "Endarteritis as a Cause of Sudden Death," 'Nordisch. Med. Arch.,' Bd. xix 'Sajous's Annual,' Nos. 11 and 15.

† See Stengel, *loc. cit*

hyperplasia, or with the atrophic forms of degeneration. Atheroma is molecular decay of the artery, and begins as milky patches in the subendothelial tissue. It may therefore be put on one side, for it is not degeneration in the sense in which the word is now being used. It is only of interest to us in that it is found more often in the sclerosed than in the normal artery.

So far as we are concerned there are three varieties of degeneration of the arterial system. The first is that form of degeneration with hyperplasia which is sometimes secondary to functional overgrowth (hypermyotrophy); the next consists in fibrous transformation of the arterial coats; and the third is calcareous degeneration.

These three correspond with similar degenerations of the voluntary muscles in muscular dystrophy, for in that disease, also, there is hyperplasia which is degenerative in character, and is sometimes preceded by true (functional) overgrowth; there is also a fibrous atrophy of muscle, and in myositis ossificans we have calcareous degeneration.

In the *treatment* of arterial sclerosis alcohol, tea, coffee, and tobacco are obviously best left alone, and meat should be used only in strict moderation. Care should be taken not to partake of an excess of fluids; exercise should be neither violent nor prolonged, but frequent, moderate, and habitual.

IX

THE DISORDERS OF POST-NATAL GROWTH AND DEVELOPMENT OF THE UTERUS

In **overgrowth** of the uterus there is uniform enlargement without decrease, or with positive increase, of function. It corresponds with the overgrown thyroid of Graves's disease. **Defective development** is prone to be associated with infantilism of other parts, or of the whole body, and *vice versá*. Sexual infantilism or sterility is the termination of most of the disorders of growth and development. **Premature senile decay** may affect the whole uterus, or it may be partial and limited chiefly to the mucous membrane or to the uterine walls. It is shown mainly by qualitative changes, and prepares the ground for tumour or cancer formation.

ALL forms of diseases of growth and development of the uterus can be identified, though they are often disguised under other names.

The Disorders of Growth of the Uterus.

I. Undergrowth.

This exists when the uterus is of small size without very perceptible decline in function. The distinction between this condition and that of defective development is evidently not great, and is mainly academic.

II. Overgrowth.

Overgrowth occurs under two conditions, and is probably of two kinds. It may arise during adolescence and represent an exaggerated impulse of rising development. Or it may not appear until middle age, when it is the expression of that loosening of the restraints of growth and development which characterises the declining periods of life.

Another division is brought about by *structural* considerations. These are three in number. In the first the overgrowth is mainly, or

solely, of the uterine muscle; in the second the overgrowth is chiefly of the mucous membrane; and in the third both of these structures are implicated together.

When the *overgrowth* is *of the muscle alone* menstruation is not usually affected. If menstruation should happen to be in abeyance, and the part should be submitted to examination, all the components requisite for a mortifying error of diagnosis are present.

We call to mind one such case in which a young married woman, who had borne her first baby, and was eagerly looking forward to the birth of a second, ceased to menstruate. The doctor who attended her found the uterus enlarged, and was at first inclined to believe that his patient was pregnant, but as there were no other indications of pregnancy he waited for a few weeks, and then asked us to see her in consultation. The uterus was then uniformly enlarged to a size which was about equal to that usual between the second and third months of gestation, but after taking all circumstances into consideration we agreed that she was not pregnant, and told the lady and her friends that her condition was due to general enlargement of the womb.

The lady now consulted a well-known gynæcologist of deservedly high reputation, and this specialist, after a careful examination, pronounced her undoubtedly between two and three months gone with child. She went home greatly pleased with this opinion, and made every preparation for the forthcoming event. Moreover, as she was a member of a numerous family and widely known, the expected accouchement was also anticipated by a large number of friends. Great, therefore, was her disappointment and chagrin when her menstrual periods reappeared, and combined with other circumstances to prove that the pregnancy was a myth. Acting upon our advice she now again sought an interview with the gynæcologist, who said that the fœtus had no doubt been expelled, and that had the cloths been more carefully examined the products of conception would have been discovered.

We have to confess to having made as bad a mistake ourselves. In the early days of general practice a single lady, aged 19 years, was brought to us by her mother to be treated for vomiting. Finding that the sickness had recurred at daily intervals during the previous week, we naturally asked as to the menstrual history, and finding that this function had been in abeyance for some ten days an examination of the uterus was suggested. The uterus was found to be without doubt slightly enlarged. At the same time the girl seemed to be a little chlorotic, and there were no other signs of pregnancy. On questioning the girl, who was a Roman Catholic, it seemed that she had only lately arrived in England from South America, and that while on the ship one of the ship's officers had behaved so very rudely that she had complained of his conduct to the lady under whose care she had been placed. Upon being told that there was evidence that she was *enceinte* she at once said that there was no doubt that the man referred to was the

father of the child. Just at this point we caught sight of the carriage of an elderly physician, now dead, standing at a house opposite. Upon calling him over, he went into the case, examined the girl, and confirmed the diagnosis, saying that she was undoubtedly six weeks gone with child.

Subsequently, finding the lady was engaged to be married to a young man living in Algiers we advised her and her mother to write to him, stating the facts. They did so, with the result that he telegraphed for her to go out, and married her without loss of time. We did not see the mother again until more than a year had gone by. Upon asking after the daughter, the mother gave a peculiar, quizzing, side-long glance, and said that the girl had given birth to a boy about a month before. It then transpired that there had been no previous pregnancy. The girl in her innocence had supposed that the rough and unmannerly grasp of the man's arm round her waist had accounted for all that we supposed we had found, and not until after her marriage did she realise the mistake. We have every reason to believe that the account given by the mother was correct.

The distinguishing feature of an overgrown uterus of this type is a uniform enlargement, occurring in an otherwise healthy woman, during the early child-bearing period, usually first observed subsequent to a pregnancy, either without symptoms, or associated with slight dragging pains, with amenorrhœa, or with menorrhagia.

Overgrowth of the whole uterus, that is, of muscle and mucous membrane together, has a similar effect to similar overgrowth of any other organ, namely, functional excess. And just as overgrowth of the thyroid gland produces the symptoms known as Graves's disease, so overgrowth of the whole uterus reveals itself in menorrhagia. Functional hyperplasia of the uterus of this sort is often associated with similar overgrowth of the blood, termed "chlorosis" (see p. 371), and it seems highly probable that the loss of blood which is often considered to be the cause of the "anæmia" is, in reality, of a salutary nature.

From the point of view of **origin** two forms of overgrowth can be distinguished. In the one, which is a *minor variation*, the enlargement is definitely the result of causes, of which pregnancy and microbial intoxication (metritis) are the chief. It is doubtful whether normal pregnancy alone can account for this form of hyperplasia. Probably there must always be some definitely pathological influence as well. This factor would be provided by microbial contamination at the time of childbirth or afterwards, or perhaps by passive congestion with retention of the products of involution, such as may occur in too long or too complete stagnation in bed during the lying-in period. Another cause of this form of

overgrowth is the local congestion which results from unnatural interference with the act of conception.

Overgrowth as a *major variation* is due to no such causes, but comes on spontaneously. Though it may appear, it is true, during one of the impulses of normal uterine growth, these can hardly be regarded as causes in the pathological sense of the word. As we have already seen, the uterus is by no means singular in the way in which it occasionally yields too easily to the pressure of developmental tides and finds itself in abnormal advance of other organs. Thus we know that parenchymatous goitre often first shows itself during adolescence as the result of normal growth changes carried to an abnormal excess. So, also, hyperplasia of the uterus may arise "spontaneously," as the result of a similar hyper-activity of the uterus at the same time of life. We have seen it in young unmarried women, and also in those recently married, as well as in those who have passed through a perfectly normal childbirth and lactation. It is probably correct to regard the enlargement in all such cases as a major variation.

The overgrown uterus of the regressive periods corresponds with that parenchymatous enlargement of the thyroid gland which occurs during the same time of life. When the mucous membrane is implicated menorrhagia is very likely to take place, but when the hyperplasia affects the muscle alone the only indication of the abnormality may be a moderate enlargement of the uterus. It is liable to become the seat of fibro-myomata and to end in degenerative hyperplasia. It is, indeed, often impossible positively to say whether, in a particular case of hyperplasia, the enlargement is uniform, and should be termed "overgrowth," or whether it is unequal, and the fibrous tissue is unduly increased, constituting degenerative overgrowth. Overgrowth of the uterus is often termed "sub-involution"; and is also, but less correctly, put down to inflammation, though this mistake is no doubt more often made when the enlargement is due to degeneration.

The Disorders of Development of the Uterus.

1. Infantilism.

The uterus may be merely of backward development, so that it is smaller than usual, and menstruation is delayed. The organ only awaits the impetus given by a normal reproductive stimulus in order to enlarge and fulfil its purpose in an ordinary manner.

In all probability the disease infantilism can only be said to exist when, with a small or miniature uterus, there is obvious incapacity, so that menstruation is either absent, or is seriously delayed, and ends long before its time. As a rule there is sterility, but it is possible that a uterus may be in a state of mild infantilism, and yet be capable of providing a temporary resting-place for the ovum. It is, however, highly improbable that a pathological defect of development should permit the fœtus to arrive at maturity.

Infantilism of the uterus is generally associated with similar imperfection of the uterine appendages; and, almost as frequently, with the "infantile pelvis" of the obstetrician. The breasts also may be of defective development, but less often, the frequency of occurrence of the associated defect diminishing as the correlated organ recedes from the physiological precincts of the uterus.

But the chief importance of infantilism of the uterus, or of the sex organs as a whole, lies in the way in which it is brought about by the infantilism of organs widely removed from them from a physiological standpoint. The existence of sex is of so much importance, and goes back to such a remote vista of evolutionary time, that the welfare of almost every organ in the body is bound up with it; the nervous, muscular, cardio-vascular, hæmic, and even the skeletal system are all responsive to the exactions of sex, and are dependent upon sex for their future existence. Hence the permanent failure of any organ is prone to be associated with sterility, or with some still more pronounced defect of the sex organs. This association is most common in derangements of the nervous system, and the earlier in life the nervous defect occurs, and the graver its nature, the more surely is the reproductive system implicated.

But the sterility, or defective development, of the uterus and other sex organs is not only a concomitant of *defects* of other organs. Sexual deficiency also comes to pass when these other organs degenerate, or, indeed, when they are merely overgrown. In short, we may say that any grave disorder of growth or development is liable to impair the fertility of the individual affected. Overgrowth of the blood, or chlorosis, is often associated with delayed development, or even with infantilism of the uterus. Genius, or overgrowth of brain faculties, is apt to be discounted by sterility, as Lombroso has shown; and it is highly probable that the same may be said of Graves's disease. And as for the degenerations, we need only mention Bright's disease, cirrhosis of the liver, pernicious anæmia, leukæmia to be reminded of the rule, seldom infringed, that senilism and sterility are reciprocal.

II. Senilism.

The varieties of *degenerative hyperplasia* are chiefly three, namely, (1) glandular, (2) interstitial, and (3) mixed.

The *glandular* variety usually goes by the name of "endometritis," but the sole claim that it possesses to this designation consists in the degenerated epithelium being more liable to succumb to the attacks of micro-organisms than is the healthy mucous membrane. The disease itself is not an inflammation, though it paves the way for it.

The mucous membrane is thicker than usual; the glands are enlarged, are prone to throw out branches from their sides, and sometimes project as a coarse roughness on the surface, producing small fungous prominences, or polypoid outgrowths, or cysts.

So far as symptoms are concerned, the main distinguishing feature of this variety is menorrhagia.

The *interstitial*, or muscular form, is usually termed "metritis," and its chief symptoms are solely the outcome of increased weight and bulk.

But the most common form is the *mixed glandular and muscular*, and it is to this that the following remarks particularly apply.

Degenerative Hyperplasia.

There is reason to believe that this disease is often mistaken for the results of inflammation (chronic endometritis, metritis), or for simple overgrowth or cancer. Just as hypertrophic cirrhosis of the liver was at one time regarded as a chronic inflammation, and as the large white kidney is still occasionally termed "nephritis," so the enlarged and degenerated uterus is said to be an inflamed uterus.

The disease is most likely to appear in those women who have borne children or have had miscarriages, for the reason that under such circumstances the uterus has undergone great fluctuations of growth and development, and is therefore more prone to disorder. But it sometimes comes on in those who have never been pregnant, and in whom there can be traced no sign of gonorrhœa or other infection. It may set in at any time of the reproductive period of life, but is most frequently met with during the last third of these periods. As a rule there is menorrhagia, due to the thickening of the endometrium, and it is in consequence sometimes believed to be cancerous. Indeed, it is not always possible to distinguish between

the big, degenerated uterus, and the uterus which is affected with widespread cancerous infiltration of its body, especially if the disease occur at about the time of the menopause, and is not discovered until a little later. We have ourselves known of an instance in which such a hyperplastic uterus was removed in mistake for a cancerous uterus. This error occurred in the practice of a skilled gynaecologist, and it is well known that such mistakes have often been made.

But sometimes, instead of menorrhagia, there is amenorrhœa, and then the disease is liable to be mistaken for pregnancy, particularly if it occur during the child-bearing period.

Though not itself malignant there is reason to believe that it favours the appearance of carcinoma, for the great increase in the size of the uterus that goes with some cancers cannot always be accounted for, either by the outgrowths of cancer, by the presence of metritis, or by the irritation of the growth. A small cancer may be found in a large uterus under circumstances which are highly suggestive of the enlargement having preceded the cancer.

The enlarged and degenerated uterus is also liable to outgrowths of fibro-myomata. Indeed, the disorder so shades off into tumour formation, that at the bedside examination of some patients it is impossible to say whether the uterus has undergone mere degenerative hyperplasia, or is the seat of diffuse fibro-myomata, and this difficulty may not entirely disappear when the uterus is inspected. But as a rule the myomata are scattered, and seem to bear the same relation to the enlarged uterus that thyroid adenomata bear to the goitrous thyroid. It is often supposed that a myoma gives rise to "hypertrophy" of the uterus by acting as a foreign body and an irritant to that organ. But this is very unlikely, seeing that in a very big uterus the myomata may be so situated that their irritant action must be of the slightest. Moreover, in some cases, with tumours of small and moderate size, the overgrowth of the uterus may be enormous, as in one reported by Kelly, where the uterus, when separated from a myoma of moderate size, weighed 645 grm., the normal weight being 46 grm. It is far more likely that the generalised hyperplasia of the uterus gives rise secondarily to the local overgrowth of the myoma. But sometimes growths of an innocent nature occur in the mucous membrane. These adenomata may be confined to the mucous membrane, but as a rule they are associated with some local overgrowth of the adjacent myometrium, constituting adeno-myomata. They are often mistaken for "fibroids." Though perfectly innocent they are more unstable

than normal uterine tissue, and are liable to degenerate into adenocarcinomata.*

On microscopic examination the degeneration may be seen to affect the myometrium alone, so that the muscle is sprinkled with lymphocytes or fibroblasts. Such changes are usually attributed to inflammation, but they are of just such a nature as those which we have met with in other degenerated organs, and are almost certainly degenerate rather than defensive. They indicate presenile retrogression (senilism), and not resistance to micro-organisms. This is proved by their after-history, which consists in peripheral absorption of the muscle elements, the formation of new fibrous tissue, the wasting and contraction of the muscle and glands, and a final shrinkage to the ordinary senile condition.

The condition of the epithelial lining of the uterus in ordinary proliferating endometritis, as described by Adami,† is in all essential respects identical with that which goes on in another tubular organ, namely, the kidney, under similar circumstances, and is known as desquamative nephritis. This so-called endometritis may also be either glandular (desquamative) or interstitial.

In the *ordinary proliferating*, or, so to say, desquamative form, "the gland tubules are enlarged, often lengthened and tortuous, and present numerous irregular dilatations even to the extent of cyst-formation. . . . The epithelial cells have in great part lost their cilia, and are clear, swollen, and mucoid. Active mitosis is also going on. The lumen of the ducts is filled with mucus, desquamated epithelium, and leucocytes. The interstitial stroma is infiltrated with leucocytes, and shows proliferation both of the cellular elements and fibrous tissue."

Put into other words there is a generalised retrogression or degeneration of tissue, manifested by molecular decay and proliferative activity, and calling forth an influx of phagocytes. Casts of degenerated cells, cell products, and phagocytic lymphocytes fill the tubules, but, there being no flushing apparatus behind them, are not washed out, as is the case with the similar casts in the corresponding disease of the kidneys.

At the same time there is more or less proliferation of connective tissue corresponding with that seen in parenchymatous "nephritis," shown by the presence of fibroblasts and by increase of fibrous tissue.

Sometimes, as in the case of the kidney, these fibrous changes

* For an account of these growths see 'Adeno-Myome des Uterus,' by Dr. Cullen, of the Johns Hopkins Hospital, published by Hirschwald, of Berlin.

† 'The Principles of Pathology,' vol. ii, p. 828.

predominate over the epithelial, giving rise to the so-called *interstitial* form of endometritis.

This correspondence with kidney degeneration is still further shown in the subsequent course of the degeneration. "In the later stages of the disease a form of atrophy may set in not unlike senile involution. The mucosa becomes smooth and thin, often pigmented, and is firmer and more fibrous than normal. Not infrequently it contains cysts about the size of a pin-head, containing a clear or slightly turbid fluid (*endometritis chronica cystica*). Microscopically there is proliferation of the stroma with the production of dense fibrous or scar-tissue. This leads to atrophy of the gland-tubules with contraction of certain sections of them, so that they become dilated." *

The identity of this process with that which gives rise to chronic interstitial "nephritis" is obvious.

Degenerative hypoplasia may be a primary condition, the result of premature atrophic changes occurring in the normal organ. At other times it is said to arise secondarily to degenerative hyperplasia (so-called metritis), much as the hypoplastic kidney is said to arise out of the large white. There can be no doubt that the hyperplastic mucous membrane does shrink, after this fashion, and in all likelihood the hyperplastic muscle undergoes a similar reduction, until nothing but old extinct fibrous tissue is left.

* Adami, 'The Principles of Pathology,' vol. ii, p. 828.

SECTION III

The Cellular or Parenchymatous Group

The Disorders of Post-natal Growth and Development of the Blood and Blood-forming Organs

I

INTRODUCTION

BEFORE entering upon the subject of this section it is necessary to insist that this is not primarily a treatise on any particular diseases of any particular organs, but deals, in the first place, with the general topic of the derangement of growth and of development to which they serve as illustrations. It has chanced that, in the pursuit of this object, we encroach upon a domain which is now being thoroughly and minutely explored by expert investigators. But their work is done almost entirely from the pathological aspect, and this same domain is capable of being approached, however crudely and imperfectly, from the biological side, regarding diseases less as diseases than as manifestations of a natural process.

Disease may, indeed, be looked upon as a gloomy and forbidding forest, with whose swamps and deserts, flora and fauna, we have become familiar through the exertions of hosts of careful and intrepid explorers. But the same forest presents a very different aspect to the man who looks down upon it from the wider perspective of a balloon, and regards it less as the abode of misery and death than as a picturesque detail in a far wider scheme. It is from this latter or more comprehensive point of view that we approach the subject which is before us now.

The cellular nature of the parenchymatous degenerations has tended to obscure their resemblance to those which are fibrous.

The process which leads to a soft accumulation of round-cells in leukæmic blood, and that which gives rise to the tough, leathery fibrosis of the liver or kidneys, seem to be widely different, not only in point of detail, but also in their very nature. Yet such need not necessarily be the case. Thus we already recognise that a "scirrhus" cancer of the breast may be even more fibrous, dense, and hard than a "cirrhosis" of the liver; and an "encephaloid" cancer of the breast may be softer and more cellular than a leukæmic spleen; yet both the scirrhus and the encephaloid are examples of the same kind of degeneration. Moreover, we also recognise that the lymph-glands in Hodgkin's disease or the spleen in splenic leukæmia may be either as soft as brain or as hard as marble, and yet be affected with the same form of disease.

Evidently, therefore, there is nothing in the mere consistency or texture of a fibrous organ that need cause us to regard it as essentially different from the organ which is soft and cellular.

As a matter of fact the difference between hardness and softness, fibres and cells, can be accounted for by the mere accident of circumstances—of age and locality—alone.

We have to remember that senile degeneration does not necessarily consist in the formation of fibrous tissue. The fibrous tissue is in reality only a bye-product of degeneration, the essential change consisting in the regression or reversion of cells from a position of high development to one of low development.

It is also most important that we should bear in mind that those organs which have to do with the making of white blood-cells are composed of tissue far more primitive than that of which the thyroid gland, liver, or kidneys is constructed. The secretory cells of the liver, for example, are highly specialised, whereas the lymph-cells, compared with them, are mere hewers of wood and drawers of water. They are the most primitive cells of the body. Hence, while there is a wide gulf fixed between the special cells of the liver and their connective-tissue framework, there is no more than a mere shallow depression between the lymph-cells of the spleen or lymph-gland and the connective tissue which holds them together. Indeed, so slight is the distinction between them that the connective-tissue cells supplement the work of the ordinary lymphocytes, for one of the duties of fibroblasts is to take on the form of lymphoid cells, and to act as phagocytes in local invasions. And this fact must needs have a very important bearing on the way in which these respective organs behave under degeneration. To degenerate means to retreat. When the division between two kinds of cells is

so wide as it is in the liver, the cells which are already of low type, do little more than proliferate, and become the round, so-called inflammatory cells, or form thick strands of fibrous tissue; whereas the same stress which brings about an increase of cells of low organisation, disorganises many of those which have already reached a high degree of specialisation. The liver-cells undergo granular and fatty changes, and present appearances which form a very conspicuous feature in microscope sections. Consequently in a liver or kidney affected with a degenerative disease many of the highly specialised cells, such as are incapable of multiplication, are gradually reduced or obliterated, and the organ tends to lose its function and to become a mere inchoate mass of cells of low type.

But when we turn to the spleen and lymph-glands, in which there are no cells of high development, we must expect to find that the marks of degeneration are much less conspicuous. Neither fatty change nor breaking down of cells will be pronounced. On the contrary, the main feature of degeneration occurring among cells already of low organisation is almost bound to consist in proliferation. Whatever function the cells possess will no doubt be defective, so that amœboid activity may be sluggish and phagocytic power lessened, but by far the most conspicuous feature will be multiplication.

Physiological.—The parts concerned in the making or storage of adult blood are the spleen, the lymphatic and thymus glands, the bone-marrow, the lympharia, and the blood itself. We have to remember that the blood is not merely a medium of communication between one part of the body and another, but is also a tissue. It is a tissue of which the cells, or cell derivatives, float in a fluid intra-cellular substance. Further, the blood is not only composed of those elements which constitute a tissue, but is also an organ, for it has functions, and these functions are peculiar to it. The blood, indeed, is as truly an organ as the liver or kidney, or any other collection of cells or tissues set apart for some special purpose. We may look upon the blood itself either as an organ, or as forming part of a more comprehensive series of organs; for, like every organ in the body, it has to be considered in relation with its feeders, or with other members of its system.

To be still more precise, the blood-forming mechanism, as a whole, is composed of two organs working separately, though mingled together. It is a double organ, for the tissues of which it is composed are of two distinct kinds—the red-blood tissues and the white-

blood tissues.* These are as widely separate in their structure and functions as the liver and the kidneys, and though necessity has embedded them together in the soft solid medulla of bone and in the fluid blood, yet they are strangers so far as community of interests is concerned.

Of these two conjoined organs the *red-blood system* is by far the more specialised, for its function consists solely in the carriage of gases from one part of the body to another. The blood-disc or erythrocyte is so single in its purpose that it has entirely lost its original form and has even ceased to be a cell, but seems in reality to be little more than a gelatinous meshwork, having its interstices filled with fluid. The uses of this sponge-like disc are, indeed, so narrowed that it has become the most completely specialised of all cells or cell derivatives, and during its short existence of three or four weeks is a mere navvy or porter and nothing else, though it is true that after it has been broken up its remains are utilised. Being devoid of a nucleus it has no power of reproduction.

On the other hand, the *white-blood system* is composed of the least specialised cells in the body. They are also the most diversified in their uses. They are the soldiers, policemen, sanitary works, plumbers, masons, for they defend the body, protect its tissues from marauders, do the low caste work of scavengers, stop leaks from the arteries and hollow viscera, and help to patch up any breaches which may be made in the continuity of the tissues.

Hence it is plain that the group of blood-making organs must be divided into two sub-groups—the white-blood organs and the red—and that these two, though mingled together, are as wide apart in their uses as any two organs in the body.

The sub-group of leucocyte-making organs is, again, capable of being separated into two divisions. These are, firstly, the great collections of lymphoid tissue termed the spleen and thymus glands, the lymph-glands, and those scattered masses which occur along the alimentary canal and in the interstices of the body, termed by Dr. Pye Smith the “lympharia.” All of these are grouped together by the character of their cells, which are of the non-granular, or lymphocyte, order.

The other division of the sub-group is found in the medulla of bone. It consists of cells of the granular order of leucocytes. These occur in the marrow in all stages of formation, from the embryonic, or giant-cell, with many nuclei, to the fully developed

* A tissue is “every aggregate of cells which obeys a common law of growth,” ‘New Syd. Soc. Lexicon.’

granular, highly amœboid, and phagocytic polymorphonuclear cell. But although the "polymorph" is the special product of the bone-marrow, this tissue is also in part the abode of the all-pervading lymphocyte. The lymphocyte, indeed, exists wherever there is lymphoid tissue.

In addition to making the granular leucocytes, the bone-marrow is also the manufactory of the red elements of the blood, and therefore contains red corpuscles in all stages of development, from the large embryonic, nucleated erythroblast to the non-nucleated and fully formed erythrocyte.

Both of these sub-groups—the white and the red—have their meeting ground in the blood, which contains elements derived from both sets of organs. Hence the blood is liable to suffer from the disorders which affect either of the tissues to which it acts as a go-between.

Pathological.—The above are the divisions and subdivisions of the blood-forming organs. We are dealing with the disease of the growth and development of organs, and regard it as an axiom that all organs capable of growth and development are also liable to undergrowth and overgrowth, to immature development and premature old age. Further, it has been shown that the criterion of a disease of either of these kinds is that we should be able to detect in its symptoms and in its anatomy certain cardinal features which correspond with the cardinal features of normal growth or development. These features will be either on a diminished or an exaggerated scale, according as the error is one of defect or excess.

Let us now see how the different primary or essential diseases of the blood serve to illustrate the truth of our proposition. We will begin with the disorders of growth and afterwards pass on to the corresponding disorders of development.

But before doing so we must premise that *defective growth* of the blood cannot as yet be separated from defective development. The former must therefore be passed over, and excessive growth of the blood will be taken first.

In correspondence with our physiological division we have excessive growth (*a*) of the red-, (*b*) of the white-blood systems, and (*c*) of the blood-tissues as a whole.

II

OVERGROWTH OF THE BLOOD

Hyperplasia of the erythrocytic organ is either the result of causes, and therefore a minor variation, or is occult and a major variation. It corresponds with the enlarged thyroid of Graves's disease and other overgrowths, and is associated with other anomalies of growth or development. Similar hyperplasia of the leucocytic organ is known as leucocytosis, and of the blood as a whole, chlorosis. All the symptoms met with in chlorosis are to be accounted for by overfulness of the blood-vessels. It is peculiarly apt to be associated with growth anomalies of the heart, arteries, and sex organs.

A. Overgrowth of the Red-blood System.

ONE of the most interesting of the overgrowths of entire organs is one which has only recently attracted attention. It is overgrowth or "hypertrophy" of the red-blood system, or "polycythæmia." It has been noticed that those who live high up on the mountains show an increase in the amount of their red corpuscles. This, to all appearance, is due to compensatory hypertrophy. The thinner air is, for the purpose of respiration, equivalent to a lessened quantity of oxygen, and to compensate for the deficiency either the lung area must be increased, the respiration accelerated, or the hæmoglobin augmented. As a matter of fact all of these events happen, and in the course of a few days, when there has been time for adjustment, a polycythæmia, or true overgrowth of the red blood, sets in. A similar condition may also result, for similar reasons, in congenital heart-disease. In that disease only a limited supply of blood can get to the tissues, and it therefore becomes necessary that the functions of the blood should be heightened. This is accomplished by means of polycythæmia.

But there is another form of overgrowth which is pathological, and its morbidity is shown by the way in which it appears without ascertainable cause, and leads to an excess vastly greater than there is any occasion for. The hyperplasia just referred to is a physiological event; that which we now come to is a malformation or disease. The polycythæmia of high altitudes is of moderate degree,

not exceeding a gross corpuscular limit of 8,000,000 per c.mm., according to Dr. Buckmaster,* whereas the pathological variety may be far more excessive. There is more than one degree of this disease. One—the more severe—is accompanied by cyanosis; of this kind nine cases have been collected by Prof. Osler, four of them having been under his own observation. The blood-count varied from 8,000,000 reds per c.mm., the hæmoglobin from 120 per cent. to 165 per cent; the leucocytes being under 10,000 per c.mm.

Polycythæmia is an affection of middle age and of both sexes. Though there is usually some enlargement of the spleen, some albuminuria, cyanosis, headache, giddiness, prostration, and the disease may terminate in coma or cerebral hæmorrhage, yet there is no reason to suppose that these constitute the morbid condition, but are merely indicative of the polycythæmia. Each, or all, of these symptoms may be absent. Considerable overgrowth of the red marrow is found after death.

An estimate of the total volume of the blood, made by Dr. Haldane, showed a large increase. The hæmoglobin in his case was more than 50 per cent. over the normal, and the actual number of the red discs was nearly double (8,000,000 to 11,000,000) the usual number per c.mm. It is expressly stated that there was no evidence of diminished destruction of red discs, yet the white cell-count showed a relative leucopenia, the leucocytes being sometimes so few as to number only from 4000 to 5000 per c.mm. Still more remarkably, there was a high percentage (66 per cent. to 81 per cent.) of polymorphonuclear cells. The blood examination, therefore, furnished evidence of abnormal activity of the red marrow, but seemed to point to some lessened activity of the cells concerned in blood destruction. On the other hand, the spleen was bigger than usual.

We must regard this disease as bearing the same relation to pernicious anæmia that parenchymatous goitre bears to fibrous goitre, the one being an overgrowth, the other a degeneration. It is interesting to note that Türk is said to have given arsenic to his patients with polycythæmia, with the apparent result of causing a considerable increase in the number of red corpuscles. In other words, the only drug which is of any real use in the degeneration of pernicious anæmia does harm in the overgrowth of polycythæmia. The use of Röntgen rays also results in a slight aggravation of

* "The Morphology of Normal and Pathological Blood," p. 39, by Dr. G. A. Buckmaster. See also Reckzeh ('Zeitschr. f. klin. Med.,' Bd. lvii, 1905, S. 215), who sums up the records of twenty-nine cases.

symptoms, apparently because of their destructive effect on the lymphocytes of the blood and spleen.

We cannot leave this subject without pointing out that though the whole of the picture presented by this condition is that of a true primary, spontaneous overgrowth of the red-blood system, there are present at the same time some traces of degeneration. It was noticed in Dr. Parkes Weber's case* that the red discs varied abnormally in size and in shape, and that normoblasts were present. These were very few, it is true, yet were decidedly more than the very scanty number present in the healthy adult. Moreover, both in his case and in Türk's the disease was *associated* with *erythromelalgia*. It is possible that this association was one of cause and effect, though Dr. Parkes Weber thinks it may have been due to mere chance. At any rate we look upon idiopathic or neuropathic erythromelalgia as coming under the denomination of a "stigma" of degeneration, and its association with idiopathic overgrowth of the blood as therefore highly suggestive of the community of origin of both these diseases.

Still more recently Drs. Hutchinson and Miller† have recorded an instance of polycythæmia in a man aged 45 years, in whom the disease was found, after death, to be associated with a high degree of *fibrosis of the heart*, together with great *thickening of the tunica adventitia* of the cardiac arterioles, and other cases of this association have been published.

B. Overgrowth of the White-Blood System: Leucocytosis.

Just as we have an overgrowth of red blood due to physiological reasons, and another overgrowth due to pathological, both distinct from that degeneration which we term "pernicious anæmia," so also we recognise a physiological leucocytosis and a pathological leucocytosis, and these are entirely different from the degeneration of leukæmia.

Physiological overgrowth of white cells is present in the newly-born child, in pregnancy, in the puerperium, and after a meal, especially if it be a full meal taken after a long fast, and be well digested. But this is not the only way in which physiological overgrowth is shown, for in truth some forms of so-called pathological leucocytosis are in reality physiological. The cause which originates them is disease, but the leucocytosis is not disease, for it is essentially due

* 'Lancet,' 1905, vol. i, p. 1251.

† *Ibid.*, 1906, vol. i, p. 744.

to a natural effort, and is a true functional hyperplasia. This may certainly be said of post-hæmorrhagic, of inflammatory, and probably of toxic leucocytosis, and is true of any leucocytosis caused by the formation of a large number of lymphocytes or of polymorpho-nuclear cells for some special end.

But true pathological leucocytosis is different, for it consists in the over-production of healthy leucocytes for no particular purpose. At least one disease answers to this description, and that is the so-called *status lymphaticus* of Paltauf, or lymphatism, which will be referred to shortly in the account of the overgrowth of that organ.

C. Overgrowth of all the Constituents of the Blood: Chlorosis.

The disease chlorosis was at one time thought to consist in a reduction in the number of the red corpuscles of the blood. It was next believed that there was no numerical increase of red elements though the hæmoglobin was defective. Now, thanks to the researches of Dr. Lorrain Smith,* it has been found that there is an actual increase of all the constituents of the blood, and that the decrease of hæmoglobin is only relative. By means of the Haldane-Smith carbon monoxide method he has been able to show that the total hæmoglobin content is normal, and that in all other respects the blood is increased in quantity, particularly in respect to the plasma and the lymphocytes, which latter undergo a slight increase beyond the other constituents. The total volume of the blood in chlorosis may amount to nearly double its usual volume.

The overgrowth, as in all disorders of growth, is not distributed impartially. Thus, as we have just seen, the hæmoglobin is increased but little, if at all, so that there is not enough to satisfy the demands of the tissues. The circulatory apparatus, distended and embarrassed with blood, is so hampered in its action that the result as regards oxygenation is the same as if there were a normal quantity of blood with deficiency of hæmoglobin, as in numerical anæmia. The plasma also is in excess as compared with the corpuscular richness. These inequalities must be regarded as either marks of degeneration or as an approach to degeneration.

In short, there is every reason to regard chlorosis as a true primary overgrowth of the blood, just as parenchymatous goitre is an overgrowth of the thyroid gland. The origin, course, and termination of chlorosis all show that it is a growth disturbance.

* 'The Morphology of Normal and Pathological Blood,' by George A. Buckmaster, p. 166.

Thus it generally makes its appearance without cause at a time of life (fourteen to seventeen years) when growth and development are in a state of exalted activity. Professor Osler says that it is sometimes hereditary. It is also remarkably fluctuant in its course, passes off without treatment if left alone, and is very recurrent. Moreover, it is prone to be *associated with anomalies of growth and development of the heart and arterial system, of the sexual system, and with overgrowth of the thyroid gland.*

The defect in the development of the sex organs is usually of a temporary nature. It is a delay, not an arrest, and the same is probably true of many cases of cardiac and arterial hypoplasia. Nothing, perhaps, points more clearly to the conclusion that chlorosis is a biological phenomenon than the fact of this association. Dr. Carl v. Noorden* says that delayed development of sex organs in boys is often associated with chlorosis in their sisters.

Chlorosis may apparently be *relative* only. Thus when it is *associated with imperfect sexual development, and with hypoplasia of the heart and blood-vessels*, it is probable that the seeming overgrowth of the blood is in reality due to its failure to adapt itself to the undergrowth or under-development of the vessels by which it is contained. Possibly in some cases of chlorosis it will eventually be found that there is actual deficiency of blood, though it may be relatively increased, having regard to the size of the blood-vessels.

Professor Senator† says that *defective development of the kidneys* as well as of the arteries is especially frequent among chlorotic girls (see p. 295).

Two circumstances in connection with its history are especially worthy of mention.

One is its tendency to disappear either spontaneously, or as the result of treatment.

The other is its exclusive devotion to the female sex. Its intimate relation with the sexual functions of women can readily be accounted for when we think of the issue of blood which takes place periodically in normal women, and the rise and fall of blood-pressure which precedes or is coincident with it. These constitute phenomena which are not represented or are insignificant in the male, and point to fluctuations in the female blood supply and to periodical adjustments which amply account for their special proclivity to excessive increase in the volume of the blood. The disease is evidently due to a loss of the normal balance, and as the

* 'Med. Klin. Wien.,' 1910, Bd. vi, S. 1.

† 'Die Erkrankungen der Nieren,' 2te Aufl., 1902, S. 302.

blood as an organ is so much more impressionable than the solid organs of the body, the morbid overgrowth not only takes place very readily, but tends to be reduced to the normal general level much more easily than when a solid organ is concerned.

It is to be noted that though chlorosis is often spontaneous in its appearance, it also has *causes*, and these consist, as a rule, in bad hygienic conditions of some sort. The disorder seems peculiarly prone to attack maid-servants who do not get enough fresh air, sunshine, and out-door exercise. The "internal environment" implied in improper food and in constipation also tend to bring on the disease.

The *symptoms* of chlorosis which seem to be best accounted for by the blood overgrowth are the dilation and palpitation of the heart, feeble circulation, softness and fulness of the pulse, œdema, venous pulsation, hæmorrhages from the nose, stomach, and uterus, sense of fulness in the head, optic neuritis, and the abundant and watery urine.

In view of the irregular temperatures which occur in pernicious anæmia and in the other degenerative blood diseases, it is of interest that chlorosis is also prone to be accompanied by similar attacks of fever.

Chlorosis is one of those diseases which were understood as well, or better, 300 years ago than they were yesterday, or until recent discoveries enlightened us as to their true nature. Dr. John Mowbray, writing in 1730, in a book entitled 'The Female Physician,' attributes it to "a vicious Concoction and Sanguification; and consequently a Collection of crude Humours, which excite various Symptoms thro' all Parts of the Body. And it commonly happens, that an irregular or improper Way of Living, especially about the Time of Puberty, or in the Time of the natural Course, engenders a pituitous and viscid Blood." Chlorosis was then termed the "icterus albus," "green-sickness," or, still more significantly, the "virgin disease" or "virgin-fever," or "febris amatoria," and the same writer describes it as follows: "The Virgin Disease is a Change of the natural Colour of the Face into a pallid greenish Tincture, with a Dejection of Strength, Gravity of all the Members and Parts of the Body, Fastidiness of Victuals, Malaria or Pica, Heaviness and Palpitation of Heart, Difficulty of Breathing, a slow Fever, Pains of the Head, Melancholy, Inflammations, and Oedematous Tumours of the Feet, Legs, Eyelids, and the whole Face; with a frigid Intemperature and Cachexy of the whole Body: proceeding from a deprav'd Nutrition, and the Abundance of crude Humours"

In respect to *treatment*, it is of interest that arsenic, which is occasionally so helpful when given for pernicious anæmia and other degenerations, is of no use, or is positively harmful, in chlorosis.

The Two Varieties of Chlorosis.

The usual age for the appearance of chlorosis is during adolescence, but it is recognised by many authorities that, after becoming decidedly uncommon as adolescence recedes, it again temporarily increases in frequency at about the time of the menopause. Hence the disease tends to favour the two extremes of female sexual life. The interpretation we put upon these facts is that the blood overgrowth of puberty represents a normal impulse of blood growth carried to an abnormal excess, whereas the overgrowth of the menopause is, in the first place, degenerative in character, and the result of a loosening of growth control brought about by declining development.

The former, the chlorosis of puberty, answers to the requirements of a *progressive variation*, and that of the menopause is to all appearance a *regressive variation*.

III

OVERGROWTH OF THE THYMUS GLAND, SPLEEN, AND LYMPH-GLANDS

Thymic hyperplasia or lymphatism is characterised, like Graves's disease of the thyroid, by uniform enlargement of the thymus with corresponding increase of function. The gland is probably inhibitory, and responsible for many of the peculiarities of infantile growth and metabolism, and the symptoms produced by its overgrowth are the result of these virtues becoming vices by being carried to excess. Simple overgrowth of the spleen is met with in young life under the name of splenomegaly, and is sometimes associated with rickets. Simple enlargement of the lymph-glands may also be started by irritation or other causes, or may arise spontaneously.

ON taking a general survey of our group of diseases of the blood and blood-forming organs we notice that the different divisions are prone to occur at different times of life. They closely follow in the footsteps of the physiological processes upon which they are based. Hence diseases of the red-blood forming organs will always tend to appear later than the corresponding diseases of the white-blood system. For while the red blood is connected with respiration, which is maintained without any very pronounced acceleration or depression while life lasts, the white-blood system is connected with the building up of the body and with its defence. The lymphatic system, acting partly in friendly antagonism, and partly in co-operation, with the thyroid gland, the pituitary, the sexual, and the supra-renal bodies, influences nutrition and growth. The part played by the thymus gland in this combination is, almost without doubt, that of "nutrition." It is the conservative or inhibitory organ, and, in conjunction with other lymph organs, in some unknown way holds in check the more stimulating influence of the sexual, thyroid, pituitary, and supra-renal glands. The lymphatic system is at its highest development during infancy. The blood then contains, relatively speaking, a far greater number of lymphocytes than it contains in after life, and the spleen, lymph-glands, tonsils, Peyer's patches, are all at their climax of relative growth.

The outward, visible evidence of the conservation of nutrition so produced is the fatness, chubbiness, and often the pastiness of the

normal baby, the rapid increase in weight, despite the small intake of food, and the comparatively low metabolism.

This is the time of life which is dominated by the thymus gland. This gland is now at its highest development, and in its short existence we have an epitome of the life of every other organ in the body and of the short-comings or excesses that may spoil their course. Hence, the thymus gland may not grow or develop properly. It may be altogether absent, or may remain of very small size. It may, on the other hand, degenerate prematurely, living a short life, and becoming fibrous and incapable long before its time. Or, lastly, it may grow excessively, and it is this overgrowth which forms part of the disease status lymphaticus, or lymphatism, to which we are now referring. Just as the anatomy of this disease consists in an exaggerated growth of all lymphatic and lymphoid structures, so the symptoms are often shown by an exaggeration of those features of infancy which constitute the infantile or lymphatic period of life. The baby of lymphatism is fat, well grown, dimpled, good tempered, but often pale and of a too pasty complexion. On examining the blood it is found to be rich in lymphocytes; but not much can be said on this score, for very few blood examinations seem to have been made. We do not know whether this lymphocytosis is much greater than is usual during infancy, but there can be no doubt of the pallor, nor of the excessive growth of the adenoid tissue of the thymus gland, intestinal patches, lymph-glands, and other parts. The picture is, as we have said, a representation of the peculiarities of infancy in an exaggerated degree. Status lymphaticus is a disease, and is comparable with overgrowth of the thyroid gland, though the thyroid and thymus may be at opposite poles in regard to their functions. Overgrowth of the thyroid gland is, as we all know, also most likely to set in at the time of greatest physiological thyroid activity. The penalty of overgrowth of the thyroid gland is Graves's disease, whilst the penalty attached to overgrowth of the thymus is still more severe, and consists in attacks of a syncopal nature and sudden death.

In the *treatment* of this affection in young children we have ordered foods more suitable under normal conditions for older children. Sugar, starch, and fat have been reduced in quantity and finely divided meat has been substituted, with apparently good results. There has been speedy reduction of weight without impairment of general health, and the dangerous fits of pallor and lividity have abated; but our experience of this method is as yet too small to be of any real value.

Overgrowth of the Spleen: Splenomegaly.

There are apparently two kinds of primary splenomegaly, each fundamentally different from the other; the one, simple splenomegaly, a disorder of growth; the other, splenic anæmia of adults, a degeneration.

The reasons for regarding the former, or simple splenomegaly, as a true overgrowth of the spleen are as follows:

(1) It often occurs in infancy or childhood, that is, at a time of life when the spleen, in all probability, is approaching its highest stage of development.

(2) Though cases occur for which no cause can be found, yet the disease seems to be often associated with rickets, and occasionally with congenital syphilis, or malaria.

(3) The structure of the spleen is that of an organ quantitatively enlarged, not qualitatively changed.

(4) Recovery is the rule.

On the other hand, the splenic anæmia of adult life is a disease of the declining stages of lymphatic development, is far more malignant, and is usually, if not invariably, fatal. Moreover, the changes which are found in the tissue of the spleen are those of degeneration rather than of simple overgrowth.

Were the infantile form of splenic enlargement a degeneration, and of the same nature as the adult form, we should expect the former to be the more virulent of the two, in accordance with the rule that the earlier in life a degeneration begins, the shorter its course, the more severe its effects.

There is reason to believe that simple splenomegaly is liable to pass on into degenerative hyperplasia (splenic anæmia), after the same fashion that is observed with other overgrown organs.

Overgrowth of Lymph-Glands: Lymphomata.

The lymph-glands are notoriously prone to undergo rapid and conspicuous enlargement in response to irritation. The growth is, as a rule, restrained within bounds, and subsides when no longer required. But occasionally an unnecessary luxuriance of gland tissue takes place from very slight causes, or from no cause at all.

These are true (pathological) overgrowths or innocent lymphomata. Apparently they may in course of time recede, and cause no further trouble; or, owing to increased vulnerability, they may succumb to intoxication, and either break down into abscesses or become caseous; or, in all probability, they may occasionally take a third course—they may degenerate, advance from a state of moderate to one of immoderate enlargement, and become the starting-point of Hodgkin's disease.

IV

THE DEVELOPMENTAL DISEASES OF THE BLOOD ORGANS. DEFECTIVE DEVELOPMENT OR INFANTILISM

Fibrosis of the spleen is sometimes consecutive to defective development. So also aplastic anæmia seems to be a similar degeneration, the result of a prior infantilism of the erythrocytic organs.

PRIMARY defective development of the lesser lymphoid structures is of no practical importance, because other parts of the lymphoid system take on their work. Such defects have, in consequence, attracted very little attention.

The *spleen* may be absent without any perceptible consequences. Dr. Thomas Saville* has recorded a case in which the spleen was less than 1 drm. (4 grm.) in weight, was firm on section, and showed increase in fibrous tissue. He mentions six other cases of defective development reported by other writers. This infantile spleen is apparently very prone to degenerate, for he goes on to say that "in some cases it appears, like cirrhosis of the liver, to be consequent on an interstitial growth of fibrous tissue." From this it might be inferred that the fibrosis is the cause of the smallness of the spleen, but it seems much more likely that this sequence is reversed—that the organ does not fully develop, and degenerates as the result of its infantilism.

One obstacle that lies in the way of definite statements on the subject is the difficulty in deciding in any given case as to whether the smallness of an organ is spontaneous, that is, due to a primary imperfection, or is the result of some previous cause. Thus, in marasmus or athrepsia the lymphoid structures of the body are sometimes found much smaller than usual. This is commonly thought to be merely part of the general emaciation, and to be due to some defect in digestion. But it is conceivable that occasionally the cart is in this case put before the horse, and that a primary

* 'Lancet,' 1890, vol. ii, p. 170.

defect of growth or development of the lymphatic structures may sometimes give rise both to the indigestion and the wasting. This will seem more likely when we call to mind that one of the features of the opposite condition—of lymphatic overgrowth, or “status lymphaticus”—is an unusual fatness and bigness of the whole body, and if overgrowth give rise to overgrowth, what is more likely than that the reverse may take place, and that wasting of lymphoid tissue sometimes precedes the general wasting and is the cause of it?

Infantilism of the Red-blood Forming Organs: Aplastic Anæmia.

Cabot,* under the heading of “fatal anæmia with hypoplastic marrow,” describes what is, to all appearances, an infantilism of the red-blood forming organs, with consecutive degeneration. The first case was recorded by Ehrlich in 1888 in a girl, aged 21 years, with multiple hemorrhages, which caused death within thirty days from the appearance of the first symptom. “The blood examined showed 213,360 red cells—small, fairly stained forms predominating. Deformities were slight; no nucleated red cells could be found despite many hours’ search before and after death. Leucocytes numbered 200 per c.mm.—an astonishing leucopenia. Eighty per cent. of these white cells were lymphocytes and 6 per cent. large mononuclears, leaving but 14 per cent., or 28 per c.mm., of polynuclear neutrophilic cells. In other words the neutrophiles were reduced to about $\frac{1}{17}$ of their normal number, while the lymphocytes were distinctly, though less markedly, diminished; eosinophiles were wanting altogether.” The marrow of a femur was found to be yellow throughout, except for a tinge of red near the lower end.

Cabot says that similar cases have lately been reported by Lepowsky† and by Muir.‡ In all three cases the disease was dubbed “purpura hæmorrhagica.”

Two other instances of aplastic anæmia are also described by Dr. Zeri,§ one of them followed by a *post-mortem* examination.

The salient features of the disease as revealed in Cabot’s and other cases are a very conspicuous paucity of red cells (less than a quarter of a million per c.mm. in Cabot’s case), with slight deformation and complete absence of embryonic forms. Leucopenia is very pronounced, but there is a relative increase of lymphocytes and

* ‘Clinical Examination of the Blood,’ p. 152.

† ‘Deutsch. med. Wochenschr.’ 1900, Bd. xxvi, p. 340.

‡ ‘Brit. Med. Journ.’ 1900, vol. ii, p. 910.

§ ‘Il Policlinico,’ July, 1905, anno. xii, p. 289.

large mononuclears. Eosinophiles are absent. The morphological features seem to be distinctly in favour of the view that the red marrow has undergone a form of degeneration, which consists in a reversion of red to yellow without any embryonic decadence in the direction of a formation of normoblasts. The reversion, in fact, keeps strictly to the lines which are so often followed by old age in an organ of imperfect development. It is probably the terminal stage of a slow unostentatious degeneration. There is little, if any, hyperplasia of cells of higher type, but plenty of connective-tissue proliferation.

Aplastic anaemia is a "disease type of young persons, women being more often affected than men, running a rapid and progressive course without any remissions of improvement, death usually occurring in the course of a few months."*

* Dr. Bierring, 'Internat. Clinics,' vol. iv, S. 19, p. 67.

V

PREMATURE DEGENERATION, OR SENILISM OF THE BLOOD ORGANS

The leucocytes with which we are chiefly concerned are the mononuclear and lymphocyte. In leukæmia the qualitative blood changes are of more importance from a pathological standpoint than the quantitative. The excess of leucocytes in leukæmia and the deficiency of erythrocytes in pernicious anæmia mislead us into thinking their pathology is different, whereas they are essentially similar.

In **leukæmia** there is an excessive formation of whites with diminished destruction (due to the degeneration of the phagocytes). In **pernicious anæmia** there is an excessive formation of reds with increased destruction. This destruction is due to the increase of inferior and therefore destructible reds on the one hand, and to unimpairment of the destroying whites on the other.

The two diseases are also clinically similar, both being "idiopathic," sporadic, with endemic tendencies, progressive, but intermittent, pernicious, and fatal. Both are attended with capricious fever.

Lymphatic anæmia (Hodgkin's disease) is analogous with **splenic anæmia**.

The **varieties** of the degenerations of the blood organs are infinite, and are based upon physiological grounds of structure, function, age, heredity, and cause.

Clinical characters.—In respect to *causation* each disease is capable of being divided into two groups, according to whether a cause can or cannot be traced. Among causes the chief are mental depression, lead, syphilis, alcohol, and other toxins, such as those of malaria, enteric, and other infectious fevers. In respect to *age*, Hodgkin's disease comes first, then leukæmia, and then pernicious anæmia. All are *progressive* and remittent. The occurrence of *heredity*, unless as transforming heredity, cannot be proved, except in splenic anæmia. The blood degenerations are associated by *correlation* chiefly with degenerations of the liver, kidneys, stomach, spinal cord. The degenerations of the white blood organs are intimately related to the sarcomas and endotheliomas.

I. Leukæmia ; Pernicious Anæmia ; Leukanæmia.

BEFORE entering upon the subject of the fate of the blood-corpuscles in leukæmia or pernicious anæmia, it is necessary to say a few more words on the physiological side, especially in respect to the leucocytes.

Physiological.

In health the white cells apparently pass rapidly from the immature to the mature condition. They live only a few days, and the breaking up of worn-out or otherwise imperfect leucocytes seems to be the work of the large lymphocytes and their congeners in the spleen and medulla. These large lymphocytes combine the functions of the police and sanitary officers of the body politic. They clear away refuse cells of all kinds, wherever found, and are the "macrophages"* of Metchnikoff. Besides acting as the scavengers of the body they are to some extent capable of dealing with the less dangerous invasions of micro-organisms.

Roughly speaking the only other phagocytic blood-cell is the polymorphonuclear or "polymorph"—the "microphage" of Metchnikoff. This is the most highly phagocytic of all blood-cells, and its special office is to repel invasions of the more virulent types of bacteria. It is the soldier cell of the body, and its presence in large numbers (leucocytosis) in appendicitis, septicæmia, or other septic disease is of good omen.

Dr. Holmes, in a thesis† on "the behaviour of leucocytes under the influence of certain bacterial and other substances," shows that the result of experiments is to prove that the toxins when injected into the blood act in the same way as the living bacteria themselves in giving rise to a pure polymorphonuclear leucocytosis, whereas the presence in the blood of non-toxic dead material (such as animal cells, red blood-discs, bacteria, or toxins destroyed by heat) produces a mononuclear leucocytosis.

The outcome of all the work that has been done on the leucocytes is, in short, to show that they are graded in respect to their phagocytic properties, the polymorphs taking the first place, the large mononuclears coming next, then the ordinary large lymphocytes, and lastly the small lymphocytes. And there is reason to believe that this also is their developmental status, the polymorphs being the most highly differentiated or advanced in the scale of development, and the small lymphocytes the least advanced. Though the polymorphs and the lymphocytes diverge both in struc-

* To be more precise, the macrophages comprise both the large lymphocytes and the mononuclears, but, though of different origin, the mononuclears correspond so closely with the large lymphocytes both in structure and in function that they may be grouped together.

† 'Guy's Hospital Reports,' vol. lix, 1905, p. 155.

ture and in function, it is the opinion of Gulland that both come from the same stock, the primitive cell being a non-granular cell of the lymphocyte order.

Therefore, for the purpose we have in view, there are two kinds of leucocytes.

One is the granular cell, or "polymorph," whose birth-place and habitat is the bone-marrow, and is the phagocyte of invading microbes, its embryonic form being the non-phagocytic myelocyte.

The other is the non-granular cell—the mononuclear "lymphocyte"—whose chief home and manufactory is in the lymph-glands, spleen, and lympharia. It is the scavenger cell, giving its principal care to the destruction of the inert refuse of the body, clearing away the *débris* of cells, and having as its embryonic form the small lymphocyte.

Pathological.

The Leucocytes in Disease: Leukæmia.

In the various forms of *leukæmia* the relations between the different kinds of cells are altered, so that as a rule there is no longer a preponderance of polymorphs. It has been pointed out that the character of the leucocytes present is of more importance in determining the nature of a blood disorder than their number. Therefore it is quite possible, and, indeed, sometimes actually happens, that the blood of a patient affected with leukæmia shows fewer white corpuscles than there are in a mild degree of leucocytosis. Obviously the quality of the blood change in leukæmia is a subject of great importance. It is not only helpful in diagnosis, but is also of use in assisting us to decide as to the pathology of the blood diseases. It serves as an indication that there is a radical difference between those changes which set up a leucocytosis, and those which are responsible for leukæmia, so that we are justified in saying that if leucocytosis be an indication of the physiological reaction of the organism to injury by invading toxic bacteria, or by toxins, we are bound *per contra* to look upon leukæmia as a condition which is emphatically not produced in this way. In other words, if we see in leucocytosis a condition which is equivalent to inflammation or hypertrophy, we, by the same token, recognise in leukæmia a degeneration or a new growth. This will be more apparent when we consider what are the changes met with in leukæmia.

Connection between the Different Forms of Primary Blood Degeneration.

We have seen that the class of diseases we term "primary degenerations of the blood and blood-forming organs" divides itself naturally into two sub-classes, one of which comprises the diseases of the white blood and white-blood forming organs, the other those of the red blood and the red-blood forming organs. The former division includes leukæmia and the splenic and lymphatic anæmias; the latter pernicious anæmia in its various forms. The differences between these two groups are so well known that there is no necessity to allude to them here. We are now concerned only with their points of resemblance, which are very close.

Thus, in the first place, there is in both cases immense proliferation or overgrowth of cells. The results of this overgrowth are seen both in the blood itself and in the blood-making organs.

Nothing in disease is more striking than the enormous *increase* in number of the white corpuscles in *leukæmia*. This increase is so pronounced that it was the occasion of the term "suppuration of the blood," originally given to leukæmia by its first discoverer, Dr. Hughes Bennett.

In *pernicious anæmia*, on the other hand, the feature which most attracts attention is the conspicuous *decrease* in the number of the red corpuscles.

We are, in short, confronted with two striking facts of exactly opposite kind, one affecting the white elements, and the other the red elements of the blood; and it seems clear that any explanation which will account for them will also account for the pathology of the two diseases of which they are the most important indications.

Now it must very emphatically be pointed out that these two outstanding facts need not necessarily be antagonistic. Indeed, so far is this from being the case that there is reason to believe that a primary feature of both diseases—that is, of pernicious anæmia as well as of leukæmia—is a polycythæmia, or numerical excess of corpuscles.

So important is this point in its bearing on the essential unity of the processes which lie at the root of both morbid conditions that, in spite of anticipating what is to be said on the subject of pathology, it is requisite that these reasons should be set forth.

We must first premise that there are two ways of accounting for the excess of white cells in the blood of leukæmia.

(1) There is, firstly, an *increased output*. Certain lymph organs undergo increase in size, and this increase is undoubtedly indicative of an exalted activity, though it is also due to an accumulation of leucocytes in their interstices.

(2) In the second place, there is every reason to believe that there is *relatively diminished destruction*.

Thus in the commonest (spleno-medullary) form of leukæmia nearly a third of the leucocytes consists of non-phagocytic myelocytes. The "polymorphs" are as a rule relatively diminished, but are actually increased, but these, too, are non-phagocytic, so far as the removal of waste cells is concerned. Then there are large numbers of intermediate cells, leaving only a small percentage of true phagocytic lymphocytes.

But in lymphatic leukæmia the proportions are very different, for lymphocytes are largely in excess. As a rule these are of the small, non-phagocytic variety, but occasionally they consist principally of the large kind.

It is evident that under normal circumstances an increased proportion of large lymphocytes would indicate an increase in the capacity for dealing with effete cells and cell *débris*. But there is evidence that these large lymphocytes, and consequently the organs from which they are derived, are not capable of doing their work, but are themselves in a state of molecular decay.

Evidences of molecular degeneration.—(1) It was pointed out many years ago that the clots formed by leukæmic blood are granular and otherwise altered in quality, indicating some profound change in the character of the white cells.

(2) It was then shown that the leucocytes are so lacking in amoeboid activity that they seem to have hardly any vitality, and resemble pus rather than white blood-cells. Recent observations by Parvu and Foy* have tended to show that in myelogenous leukæmia from 50 to 70 per cent. of the polymorphs are of impaired phagocytic power; and that in acute leukæmia all the large lymphocytes are non-phagocytic, while the phagocytic power of the polymorphs is decidedly increased. In both disorders the opsonic index is diminished.

(3) Since cytology has become more accurate it has been proved by Gumprecht that many of the leucocytes of leukæmic blood show obvious signs of molecular degeneration.

(4) There can be no doubt that the activity of a cell may be seriously impaired even though no structural changes are visible.

* 'Tribune Médicale,' February 19th, 1910.

Nevertheless it has long been observed that cells of leukæmic blood are very defective in their staining properties, and that they are crushed very readily by the pressure of the cover-glass. Moreover, it is more particularly the large lymphocytes which show these evidences of deterioration. Further, the *débris* of white cells is often to be seen floating about in the plasma in such quantities as are never observed in health. All these facts are indicative of a molecular alteration of structure of such a nature as must seriously interfere with the function of the cells.

(5) After all there is no stronger proof of the complete incapacity of the leucocytes than that which is furnished by their own excess, for nothing more plainly denotes disorganisation of function than complete want of purpose. Senseless multiplication of cells is just as significant of incapacity and insanity on the part of the lymph-cells as is volubility and incoherence of language significant of insanity of brain-cells. And just in the same way that brain-cells in chronic mental insanity may show no obvious alteration in structure, so is it with some of the blood-cells in leucocytic insanity.

Moreover, the facts are in every way in keeping with clinical observation, which informs us that the subjects of leukæmia are peculiarly liable to inflammation of the pleuræ, pericardium and other parts, and also to diarrhœa and to capricious irregular fevers, all of which are highly suggestive of the attacks of micro-organisms on tissues whose power of resistance has become impaired.

Consequently there is good reason to regard the excess of white cells in leukæmia as being due to degenerative over-production of leucocytes on the one hand and to interference with their destruction on the other. At the same time it must be understood that, though relative destruction is lessened, it is probable that actual destruction is increased, for the excess of uric acid which occurs in the urine in leukæmia is commonly regarded as evidence of a breaking up of nucleins, the result of an excessive destruction of leucocytes.

Pernicious anæmia.—As leukæmia is distinguished by the enormous increase of embryonic white cells, and of forms intermediate between them and mature cells, so also is pernicious anæmia distinguished by a similar increase of embryonic red cells and of intermediate kinds.

If it is important to insist that the increase of leucocytes in leukæmia is largely the result of the phagocytes being rendered incompetent by degeneration, it is of equal importance not to overlook the fact that pernicious anæmia is a disease of the red and not

of the white blood. Hence, the natural scavenging work of the phagocytes goes on unchecked. But seeing that it is the office of the scavengers to break up and get rid of such erythrocytes as are too immature or too effete to be useful, it follows that there is not diminished destruction, but excessive destruction, in pernicious anæmia. This, no doubt, is the explanation of the fact that in pernicious anæmia the spleen becomes bigger, and that the large lymphocytes increase at the expense of the other leucocytes, for it is just these large lymphocytes, with their non-granular allies in the bone-marrow and spleen, which are the natural phagocytes of immature and used-up erythrocytes.

It may be asked, How can it be proved that in pernicious anæmia there is this virtual polycythæmia? Now, excessive blood destruction, as Dr. Hunter has shown, is indicated by excessive pigmentation of the urine and skin, and by an accumulation of iron in the liver, bone-marrow, lymph-glands and spleen; and this iron must, of course, bear some proportion to the destruction of the red corpuscles. But it is found that there is more than can be accounted for by the destruction of such a number of erythrocytes as exists in normal blood. For example, in a case recorded by Dr. Hale White* the erythrocytes at death numbered 43 per cent., but the quantity of iron was twelve times more than it ought to have been.

Stuhler† found that under ordinary conditions 100 grm. of dried liver contain 81 mgrm. of iron, or 0·081 per cent.,‡ whereas in a patient with pernicious anæmia the iron was increased to 1900 mgrm., or more than twenty-three times the normal percentage.

Dr. Hunter§ estimated the quantity of iron found in the liver and kidneys obtained from seven patients who died from pernicious anæmia, and compared them with similar estimations from the like number of cases of secondary anæmia. He found that the percentage of iron in the liver and kidneys of patients with secondary anæmia amounted to 0·079 per cent., whereas that from the same organs of cases of pernicious anæmia was nearly five times that amount, or 0·360 per cent.

On the other hand, in some undoubted instances of pernicious anæmia no excess of iron has been found in any organ. Hence it

* 'Guy's Hosp. Gaz.,' 1894, vol. viii, p. 5.

† Quoted by Lazarus, 'Nothnagel's Encyclopedia,' English translation, 'Diseases of the Blood,' p. 281.

‡ Professor Stockman finds 0·080 per cent. in healthy livers—almost exactly the same.

§ 'Lancet,' 1903, vol. i, p. 283.

is evident that the amount of iron set loose by the destruction of red discs is very variable. This by no means proves that such destruction does not take place, for there may be, and probably is, great variation among different individuals in the capacity of their organs for storing or getting rid of iron. Moreover, just as in some cases of leukæmia there is very little excess of white cells, so also in some cases of pernicious anæmia of the aplastic type there is far less proliferation than in others.

What we are certain about is that in the ordinary patient affected with pernicious anæmia there is evidence of destruction of red corpuscles, and that this destruction is so excessive as to imply an excessive formation. Moreover, a rough calculation of the waste tallies with what is revealed to the naked eye, and to the microscope, by an investigation of the centre of manufacture, *i.e.* the bone-marrow.

If this view of the origin and destiny of the nucleated red cells be correct, it is probable that the work of the lymphocytes and their allies in the spleen is of a salutary nature. The vice is in the erythroblastic tissue of the red marrow, and the destruction of red discs must be regarded as evidence of the healthy efficiency of the leucocytic tissue.

Hence, in the course of a case of pernicious anæmia, the occurrence of "showers" of nucleated red cells constituting a "blood crisis" suggests a very profound type of anæmia, and, if not speedily followed by a remission, serves as a warning of an impending breakdown.

Leukæmia and Pernicious Anæmia.

The massive accumulation of cells which occurs in both leukæmia and pernicious anæmia in the centre of manufacture constitutes another point of resemblance between them. In a typical case of spleno-medullary leukæmia the spleen and bone-marrow are conspicuously bigger than usual. So also in pernicious anæmia the increase in size of the red medulla is a very striking feature. In both cases these appearances vary exceedingly, and it occasionally happens that even in advanced disease there is very little increase in size either of the leucocyte-forming organs on the one hand or of the red medulla on the other. It is true that this can far more often be said of pernicious anæmia than of leukæmia, but this does not in reality affect our comparison, as will appear later on.

Judging from the appearance of the medulla in ordinary cases of

pernicious anæmia, we are driven to conclude that there would be a vast accumulation of erythrocytes in the blood, comparable with the accumulation of white cells in leukæmia, were it not for the excessive destruction. It must also not be forgotten that the erythrocytes which have not been destroyed carry an excess of hæmoglobin, and that much waste of hæmin derivatives takes place through channels which are not in use in a condition of health. Some are found in the substance of the kidneys and pancreas, where as a rule there is none, and there is much leakage through the excretion of the kidneys and intestines, and by means of hæmorrhages.

Then we have one other important fact tending to prove that the pathology of different members of the group is similar. In pernicious anæmia there is an increase of erythrocytes and diminution of leucocytes. In leukæmia the relations are reversed, the leucocytes being increased and the erythrocytes diminished. In splenic anæmia and lymphatic anæmia there is also a paucity of erythrocytes. To put this into one sentence, we say that where the leucocyte-forming organs are increased there is erythropenia, and where the erythrocyte-forming organs are increased there is leucopenia.

It is well known that pernicious anæmia and leukæmia also have close affinities on the clinical side. Both are "*idiopathic*" and *sporadic*, but show a tendency to favour certain localities, *i. e.* to occur *endemically*, and are sometimes brought into existence by depressing circumstances, or by *pregnancy*, or lactation. They are *progressive* in course, with *periods of intermission*; may be improved or temporarily arrested by the use of *arsenic*, or by cheerful surroundings and good sanitation in general, but are ultimately fatal. In addition both of them are prone to show apparently capricious elevations of temperature, and have other features in common, some of which will be alluded to farther on. Such facts as these are sufficient to prove that there is a close affinity between the two chief forms of primary blood disease, and that they may be safely grouped together in the same class.

II. Lymphatic Anæmia (Hodgkin's Disease) and Splenic Anæmia.

There is close resemblance between the presenile degenerations of the spleen and of the lymph-glands, and this resemblance, as in the case of similar degenerations of the white and of the red blood, is necessarily the outcome of their physiological and morphological relations.

"The spleen is practically a lymphatic gland interposed in the

blood-stream, whereas definitive lymphatic glands of the anatomist are intercalated in the lymph-stream" (Kondrad Helley).*

The spleen is, indeed, little more than a gigantic lymph-gland, or rather, a conglomeration of lymph-glands, devoted to the service impartially of the red and of the white blood.

For the red blood it acts the useful part of destructor by getting rid of the used-up red discs. It therefore undergoes physiological enlargement in pernicious anæmia.

At the same time it is essentially a leucocyte-forming organ, and therefore shares in the degenerations of the white-blood system.

Just as they may remain infantile alone, so both spleen and (more often) lymph-glands may undergo degeneration alone, no other organ being affected. The maladies are then known as lymphatic anæmia or Hodgkin's disease in the latter case, and splenic anæmia in the former.

Both diseases are characterised by enlargement, and must therefore be distinguished from their corresponding overgrowths.

In true degeneration of the spleen there is invariably some defacing alteration of structure, selecting as a rule some one tissue far more than the rest. Thus one case of splenic anæmia is remarkable for extensive fibrosis, the whole organ being conspicuously hard and tough. In another there is corresponding proliferation of the endothelial elements. In a third the Malpighian bodies are picked out for degeneration, so that all their elements are proliferated and degraded.

Making allowances for differences of structure, much the same may be said of the changes in the lymph-glands of Hodgkin's disease. Here also the morbid process is characterised by an apparently capricious lack of uniformity, leading to wide degrees of variation in the appearance of the glands in different cases.

More will be said upon this subject when we come to deal with the relations of these diseases with cancer.

Varieties.

The varieties of degeneration of the blood-forming organs are many, corresponding with their great diversity of structure and function. Variations, moreover, occur not only because of these two factors, but also as the result of age, heredity, and mode of origin.

* Dr. Batty Shaw, 'Practitioner,' vol. lxxx, 1908, p. 243.

Varieties based upon Variations of Normal Structure and Function.

Lymphatic glands.—Though Hodgkin's disease as a rule begins in the cervical glands it may start in the glands of any other part of the body, giving rise to corresponding variations in symptoms. Thus Hodgkin's disease beginning in the mediastinal or in the abdominal system of glands may for a long period be confined to that area, giving rise to a train of symptoms which is sometimes the occasion of great difficulty in diagnosis. Or it may start, not in the lymphatic glands, but in the bone-marrow, in the lymph-follicles of the intestines, in the tonsils, the lymph-tissues of the skin, or probably in any other of the collections of lymphoid tissue in the body, including the thymus gland. Each furnishes its own variety, so that we have lymphadenoma spinalis, L. cutis, L. gastro-intestinalis, chloroma, etc.

Spleen.—The chief varieties of splenic degeneration are: (1) Splenic anæmia; (2) splenic anæmia associated with hypertrophic cirrhosis of the liver (Banti's disease); (3) splenomegaly of endotheliomatous type (Gaucher).*

Bone-Marrow.—The bone-marrow is extensively involved in (1) ordinary spleno-medullary and medullary leukæmia. As the bone-marrow normally contains two forms of lymphoid cells, to wit, lymphocytic and polymorphonuclear, so also medullary leukæmia may be distinguished either by the preponderance of lymphocyte elements or of polymorphonuclear and myeloid. It is also affected in (2) pernicious anæmia and (3) osteomalacia. Yet other forms of degeneration of the bone-marrow will be referred to when we come to the subject of osteomalacia.

Blood.—Like the degenerations of the bone-marrow, those of the blood are in the main of three kinds, according as (a) the red or (b) the white or (c) both red and white are affected. These several conditions are known as pernicious anæmia, leukæmia, and leuk-anæmia.

(a) Dr. Bierring† classifies *pernicious anæmia* as—

(1) Hyperplastic or metaplastic.

(a) Erythroblastic = pernicious anæmia of ordinary type.

(b) Leucoblastic = leukæmia.

(2) Aplastic.

(3) Myelopathic.

In the rare myelopathic form the red bone-marrow is said to be

* Osler, 'Principles and Practice of Medicine,' 6th edition, p. 762.

† 'Internat. Clinics,' vol. iv, S. 19, p. 67.

pushed aside and starved by leukæmic nodules, or by some neoplastic growth.

(b) *Leukæmia* is as a rule characterised by marked hyperplasia, not only of the white elements of the blood, but also of some great lymph-cell supply organ or organs, such as the spleen, marrow, or lymph-glands. But occasionally the hyperplasia of the white blood is so predominant as to constitute almost the sole feature of the disease, the bone-marrow or spleen being very little affected.

(c) In *leukanæmia* there is degeneration of both red and white corpuscles, usually accompanied by enlargement of the spleen ; and, less often, of the lymph-glands, and of the red bone-marrow. The "reds" are greatly reduced in number, normoblasts are present, and the leucocytes are in excess and are of abnormal types and sizes.

Much difference of opinion exists as to the pathology of leukanæmia. Dr. Drysdale,* in an article on "Leukanæmia: Its Relation to Leukæmia and Pernicious Anæmia," arrives at the conclusion that the term is misleading and useless, and that "the majority of cases so far described under this head belong to the group of atypical myelopathic leukæmias."

Clinical Characters.

Ætiology.

Though all the different members of the group appear, as a rule, without obvious cause, yet there are causes, and occasionally these are decidedly influential. Thus, generally speaking, no disease seems to be more spontaneous in its appearance than *pernicious anæmia*. So seldom indeed is a satisfactory cause forthcoming that its discoverer, Addison, gave it the name of "idiopathic anæmia." Yet even pernicious anæmia may be so dependent upon causes as to occur *endemically*, for no other reason than that it is the product of factors present in one locality to a far greater degree than in another. It is to be found, for example, in certain districts in Switzerland and in Germany far more often than in Great Britain. But one of the chief causes of endemic pernicious anæmia is the prevalence of *ankylostomata* or of the *Bothriocephalus latus*. These may give rise to a form of anæmia which is indistinguishable from pernicious anæmia, and consequently *is* pernicious anæmia. Yet even in this case the cause is not by itself sufficient to produce the malady, for the parasite will

* 'Quart. Journ. Med.' vol. i, 1907, p. 88.

only give rise to pernicious anæmia in a certain proportion of cases. For a given cause to produce the true pernicious type it is necessary that there shall be another factor, this other factor being an inborn tendency to this special form of disease.

Other causes assigned for the onset of pernicious anæmia are the *shock* of an injury,* *depressing physical and mental conditions*, such as insanitation, mental depression, nervous shock. Alcohol seems to have little if any influence. Dr. Hunter attaches great importance to toxins of intestinal origin, and particularly to those which occur in connection with decayed teeth.

Among other causes of pernicious anæmia is probably *lead*, for one of the most conspicuous symptoms of lead poisoning is anæmia of oligocythæmic type, and, according to Stengel, megaloblasts, which are so especially characteristic of the pernicious form, "undoubtedly occur in lead poisoning with considerable frequency." There may also be marked poikilocytosis.

Hodgkin's disease has been attributed to *malaria*, and to the toxins of *enteric fever*, *syphilis*, *measles*, *scarlet fever*.

Leukæmia, though apparently more often spontaneous, may also have causes. Thus, Sir William Gowers found that among the reports of 150 cases investigated by him, *depressing physical or mental conditions* often preceded the disease. Alcohol intemperance was present in only 3 per cent. But of all causes *malaria* seemed to be the most effective, for no less than twenty-five of the patients had had ague. Influenza has apparently accounted for some cases. It is stated in Nothnagel's 'System' that *severe anæmia of ordinary type* may become transformed into acute leukæmia.

Age.

Age affects the blood degeneration group in two ways:

(1) In the first place certain forms of disease appear earlier than other forms.

Hodgkin's disease is usually met with between fifteen and thirty, and there can be no doubt that many cases of so-called tubercular disease in young children are in reality Hodgkin's disease. We have ourselves been present at *post-mortem* examinations on children said to have died from *tubes mesenterica* in which Hodgkin's disease was found to be the cause of death, and such an experience is apparently not exceptional.

* Professor A. H. White, 'Lancet,' 1904, vol. ii, p. 1423.

Leukæmia is a disease of early middle age, its favourite range being between thirty and forty.

Pernicious anæmia usually begins somewhat later, that is, between forty and fifty. It is very scarce in childhood.

(2) In the second place, age, as we already know, so affects the progress of any particular form of degeneration that, generally speaking, the earlier in life it appears the more rapid is its course. This is certainly true of leukæmia, Hodgkin's disease, and pernicious anæmia. Acute leukæmia occurs only in the young.*

Splenic anæmia, on the other hand, is far more deadly when it occurs in the adult than in the child. This apparent exception is, however, not an exception at all, for, as we have seen, there is good reason to believe that the splenomegaly of children is, as a rule, no more than an overgrowth of the spleen, that of the adult being a degeneration.

Course.

A conspicuous feature of *pernicious anæmia* was stereotyped by Biermer when he designated the disease "*progressive pernicious anæmia*." But it might quite as accurately be termed "*cyclical anæmia*," or "*intermittent anæmia*," for of all of the diseases with which we have to deal, none is more distinguished for its *fluctuations* of course than pernicious anæmia. These are so conspicuous and so well known as to require no further comment. But it is not so widely known that all other forms of primary degenerations of the blood-forming organs show this same feature. In *Hodgkin's disease* they are particularly easy of identification, because the manifestations of the disease are, as a rule, superficial. The whole course of Hodgkin's disease is often remarkably irregular. The enlarged lymph-glands in a certain part of the body undergo apparently spontaneous increase in size; shortly afterwards some of these same glands, or those of another group, become obviously smaller, only to swell out again later on; and so the fluctuations continue, first in one part and then in another, like the movement of waves. But now and again we can detect a more general or tidal movement, which carries the disease, as a whole, onward to a certain extent and there leaves it, or else it recedes almost to the point from which it started. Such an ebb and flow may occur many times before the final submergence takes place. We have seen these fluctuations in each one of the half-a-dozen cases of Hodgkin's disease that

* Dr. Batty Shaw, 'Practitioner,' vol. lxxx, p. 243.

have come under our observation, and they are often referred to in the clinical descriptions of instances of the disease.

According to Nothnagel's 'System of Medicine,' marked remission has been noticed in the course of acute *leukæmia* in a very few cases only. But in chronic *leukæmia* such remissions undoubtedly often occur, and form a conspicuous feature of the disease.

In *splenic anæmia* and Banti's disease periods of remission are not infrequent* and are sometimes very pronounced.

The *rate* of progress of any particular variety of blood disease varies widely. It is most often chronic, extending over some years. This is particularly the case with splenic anæmia. The course of pernicious anæmia may also be very protracted. On the other hand, *leukæmia* is, as a rule, more rapid, and so is Hodgkin's disease. We have seen *leukæmia* fatal from multiple cerebral hæmorrhages (specimens now in the Museum of the Reading Pathological Society) within a week after the first appearance of noticeable symptoms, and Hodgkin's disease may apparently begin and end within a couple of months, though, as a rule, it lasts for two or three years.

Heredity.

We can find no really satisfactory instance of the hereditary transmission of *pernicious anæmia* or of *leukæmia*, for though Dr. Gulland,† in writing on the subject of pernicious anæmia, says, "Within the last few months I have come across three cases in people in middle life whose fathers had died of pernicious anæmia, in one case ten, in another twelve, and in the third eight years before," he does not give details. Other cases which have been reported do not bear investigation.

Mr. Roger Williams‡ says that "Peacock has seen Hodgkin's disease in twin boys four years old," but gives no reference.

An example of direct and transforming heredity has just been brought to our notice. A gentleman engaged in one of the learned professions, affected with asthma, had a maternal uncle who was attended by Dr. Hurry, of Reading, for pernicious anæmia, and died from that disease in 1896 at the age of sixty-three. His mother died at sixty from "extreme nervous prostration," no other cause being known. A brother died from pernicious anæmia at twenty-six, and a sister from pernicious anæmia at about twenty. A

* G. E. Armstrong, 'Brit. Med. Journ.,' 1906, vol. ii, p. 1273.

† 'Brit. Med. Journ.,' 1907, vol. i, p. 71.

‡ 'The Natural History of Cancer,' p. 363.

maternal aunt died from Graves's disease and two brothers from diabetes, both at sixteen. There were seven other brothers and sisters, of whom five are still living. In each of these cases of pernicious anæmia the disease had first been diagnosed by a general practitioner of recognised ability and the diagnosis had been confirmed by a consulting physician.

Transforming heredity.—A remarkable case of Professor Clifford Allbutt's has already been referred to (p. 72). It is that of the occurrence of cancer, leukæmia, pernicious anæmia and pseudo-hypertrophic paralysis each in a different member of the same family.

Dr. French* also gives the abstract of a case of Dr. F. Taylor's occurring in the post-mortem records of Guy's Hospital. A girl, aged 10 years, admitted for weakness, extreme anæmia and vomiting, died two days later, apparently of pernicious anæmia; and her brother had died in the same year in the same hospital of splenic anæmia. Nothing is said in the abstract of the presence or absence of megaloblasts, and the colour index was not high. Nevertheless, the evidence in other respects, including the ferrocyanide reaction in liver and spleen, pointed to pernicious anæmia.

The form of primary blood-organ disease which is most often hereditary is *splenic anæmia*. Some cases are in all probability examples of mere overgrowth of the spleen, or spleen and liver, but others are no doubt degenerative in character. In the latter event the degeneration is probably consecutive to a previous overgrowth, undergrowth, or infantilism.

The splenic anæmia may be splenic only, or may occur in its advanced form (Banti's disease) in association with cirrhosis of the liver.†

Two cases of splenic anæmia are recorded by Dr. Frederick Taylor‡ occurring in brother and sister, and other members of the same family were said to have been affected. Yet other instances have been reported by Gilbert and Fournier and by Brill.§

Dr. Batty Shaw quotes a paper by Springthorpe,|| in which details are given of the occurrence of six cases in one family.

In the lower animals.—Pernicious anæmia has been found in the orang-outan, and leukæmia in the dog, horse, cat, pig, mouse.

* 'Guy's Hosp. Reports,' vol. lxiii, 1899, p. 156.

† Dr. Field, 'Amer. Journ. Med. Sciences,' n.s., vol. cxxv, 1903, p. 405.

‡ 'Lancet,' 1904, vol. i, p. 1555.

§ 'American Journ. Med. Sciences,' 1901, vol. cxxi, p. 377.

|| 'Intercolonial Med. Journ. of Australia,' 1904, vol. ix, p. 341.

Association with other Degenerations.

Allusion has already been made to associations between members of this group and *cirrhosis of the liver* in Banti's disease (see p. 282).

The conjunction is good evidence that both cirrhosis and splenomegaly are fundamentally of the same nature. There does not seem to be any reason to suppose that the one malady can give rise to the other, and it is still less likely that each is the result of the action of a different cause. A far more probable explanation of their conjunction is that they are instances of the same disease process acting upon different organs in a similar manner.

This is to some extent suggested by the way in which the one disease reciprocates the other. We have already seen that cirrhosis is linked on to splenomegaly by a chain of connecting diseases. The addition of the cirrhosis and splenomegaly of Banti's disease to Dr. Rolleston's series (see p. 266) would make the connection still more complete, especially if we interpose as a coupling a variety which Dr. Rolleston terms "metasplenomegalic cirrhosis," in which the splenic enlargement precedes any manifest change in the liver. We should then have cirrhosis of the liver at one end of the scale and "cirrhosis" of the spleen at the other, with all sorts of intermediate forms in between.

This connection between fibrosis of the liver and primary splenomegaly is two-fold, for while in Banti's disease the splenic enlargement is primary and the liver fibrosis secondary, in primary fibrosis of the liver the order is reversed, and it is the opinion of Oestreich* and others that the splenic enlargement is not the result of mere congestion, but is due to some process acting independently of the liver.

We also meet with cirrhosis of the liver in some instances of pernicious anæmia. Drs. Brett and Cadet† believe that this association is of frequent occurrence. They examined the livers in three consecutive cases of pernicious anæmia and found early cirrhosis (biliary) in all three.

A case is reported by Dr. W. Field‡ in which Banti's disease co-existed with the interstitial form of *Bright's disease*. Dr. Pye Smith§ published in 1875 an instance of "enlargement of the liver and spleen from overgrowth of adenoid tissue without leucæmia." The spleen weighed 83 oz. (311·85 grm.), and the point of special

* 'Virchow's Archives,' Bd. cxlii, S. 285.

† 'Lyon Médical,' 1902, p. 457.

‡ 'American Journ. Med. Sciences,' n.s., vol. cxxv, 1903, p. 405.

§ 'Trans. Path. Soc.,' vol. xxi, p. 390, and vol. xxvi, 1875, p. 199.

interest is that, while there was no fibrosis of the liver, the kidneys were granular and contracted. The case seems to have been virtually one of Banti's disease, in which the kidneys were fibrosed instead of the liver.

In short, the more we know of these diseases the more we are forced to conclude that the distinctions between them are only territorial. When we find a big degenerated spleen with numerical anæmia we say it is "splenic anæmia"; when the liver is also big and degenerated we call it "Banti's disease"; but when the kidney is affected in a similar way and not the liver our nomenclature fails, and the disease is termed "splenic anæmia with Bright's disease."

Bright's disease also sometimes occurs in company with pernicious anæmia, and no doubt many additional instances would be recorded were it not that the blood disease is usually looked upon as the direct consequence of the other. Dr. Gulland draws attention to this association,* and gives details of an example under the heading of "kidney disease masking pernicious anæmia." The patient was sent to him by a doctor, who attributed the pallor partly to the chronic Bright's disease and partly to loss of blood during parturition.

In one case of "chronic nephritis" associated with anæmia of the pernicious type and mentioned by the writer incidentally, he definitely says that in spite of the condition of the blood he cannot regard it as a case of pernicious or idiopathic anæmia, because of the presence of the kidney disease, and no doubt other similar cases are passed over for similar reasons. How many instances of pernicious anæmia are so regarded may be gathered from the fact that Dr. Gulland, in the course of a complete histological investigation of seventeen cases of pernicious anæmia, said of the kidneys, that "in every case these showed catarrhal or interstitial nephritis.†

The significance of associations, of course, increases with their frequency. The only statistics we can find on the subject are those of Sir William Gowers‡ in relation to leukæmia, and owing to the scarcity of leukæmia they were at that time necessarily derived from a small number of cases. He found that out of eighty-seven instances of splenic (splenomyelogenous) *leukæmia* in which the liver was examined, three were affected with atrophic cirrhosis, and that out of 121 cases in which the kidneys were examined, chronic

* 'Brit. Med. Journ.,' 1907, vol. i, p. 69.

† 'Journ. of Pathol.,' 1905, p. 142.

‡ Reynold's 'System of Medicine,' vol. v, p. 216.

Bright's disease was present in six. This proportion of 3·4 per cent. and 5 per cent. respectively must be far higher than could possibly be accounted for by coincidence.

Extreme (pathological) atrophy of the *supra-renal capsules* has been found by Dr. Douglas Stanley* in a patient with splenic anæmia, and a similar condition has been noticed in association with *pernicious anæmia*. One of these occurred in the practice of Dr. Wickham Legg,† and the other in that of Dr. Goodhart.‡ In yet another instance Dr. W. G. Thompson, of New York,§ mentions the occurrence of pernicious anæmia with cystic enlargement of the supra-renals.

Perhaps the most interesting associations are those of pernicious anæmia with *atrophy or fibrosis of the stomach*, with cancer of the stomach (Nothnagel, Eisenlohr),|| or with fibrous degeneration of other parts of the alimentary tract, such as the colon.¶ Professor Osler,** in describing a case of "atrophy of the stomach, with the clinical features of pernicious anæmia," occurring in a heavy drinker with a record of syphilis, refers to other cases of a similar kind, and draws attention to a remarkable overgrowth of the muscularis mucosæ as an associated condition not easy of explanation. He also mentions Nothnagel's case of cirrhotic contraction of the stomach, with atrophy of the peptic glands and great thickening of the muscularis mucosæ, and another of Fenwick's of similar fibrosis with atrophy. In Nothnagel's patient the fibrous overgrowth of the stomach wall was so extreme that that organ, when it was taken out of the body, retained its shape like a leather bottle. A similar case is referred to by Stengel in Lazarus's †† article on pernicious anæmia, in which the glandular part was much atrophied. Yet another instance of degenerative hyperplasia is recorded by Professor Nothnagel.‡‡ In some of the cases recorded the anæmia was no doubt not true pernicious anæmia; in others the characters of the anæmia tally in every important particular with those of pernicious anæmia, and it must therefore be so regarded.

* 'Lancet,' 1895, vol. i, p. 413.

† 'St. Bartholomew's Hospital Reports.'

‡ 'Trans. Path. Soc.,' 1882, vol. xxxiii, p. 340.

§ 'American Journ. Med. Sciences,' 1893, vol. cvi, p. 382.

|| 'Brit. Med. Journ.,' 1895, vol. i, p. 966.

¶ 'Dr. H. Morley Fletcher, 'Trans. Path. Soc.,' 1899, vol. l, p. 127.

** 'American Journ. Med. Sciences,' vol. xci, 1886, p. 498.

†† 'Nothnagel's Encyclopædia,' English translation, "Diseases of the Blood."

‡‡ 'Deutsches Archiv f. klin. Med.,' Bd. xxiv, 1879, S. 353.

Another well-known combination is that of *pernicious anæmia* with *fibrous degeneration of the spinal cord*, which was first recognised by Lichtheim in 1887. Many instances have now been reported. Very little has been said of the conjunction of these degenerations of the nervous system with other forms of primary anæmia, though Dr. Russel* thinks "it is possible that the association has been missed through ignorance of the possibility of such an occurrence." He then goes on to say that Eisenlohr and Müller have found lesions (sclerosis) of the peripheral cranial nerves in lymphatic *leukæmia*, and changes in the medulla oblongata have been found by Kast and Alt. Dr. Russel states that Müller has published a case of leukæmia, and Nonne two cases of the same disease associated with sclerosis of the spinal cord. These must, of course, be distinguished from those cases in which there are lymphoid deposits in the spinal cord, such as are described by Ortnier,† and considered by him to constitute a special type of "pseudo-leukæmia."

Dr. Mitchell Clarke,‡ after describing two cases of twin leukæmia and spinal sclerosis, draws attention to the fact "that extensive changes may be present in the cord without marked clinical symptoms, and that the lesions are of somewhat diverse character."

The sclerosis associated with *pernicious anæmia* is to be found, as a rule, in both posterior columns, but may be present in the lateral columns, in the anterior pyramidal, direct cerebellar, or crossed pyramidal tracts, or it may be more or less disseminated or diffuse. It may be entirely cerebral. In Dr. James Taylor's two cases§ it was in the white matter of the cord only. Sometimes the pernicious anæmia seems to come first in order of precedence; at others the cord changes appear a long time before the anæmia is recognised.||

When the coincidence of pernicious anæmia with this fibrosis of nerve tracts was first noticed, it was, of course, thought by some that the one disease must have occasioned the other. But now there is apparently a fairly general consensus of opinion that this is not the true explanation, and it is believed by Lichtheim, Minnich, Taylor and others that they have the same relation to one another that splenic anæmia has to cirrhosis of the liver in Banti's disease,

* 'Lancet,' 1898, vol. ii, p. 12.

† 'Wiener klin. Wochenschr.,' 1890, Bd. iii, S. 698.

‡ 'Brit. Med. Journ.,' 1897, vol. ii, p. 325.

§ 'Med.-Chir. Trans.,' 1895, vol. lxxviii, p. 151.

|| Dr. French, "Sixty-eight Cases of Pernicious Anæmia," 'Guy's Hosp. Reports,' vol. lxiii, 1909, p. 106

or that pernicious anæmia has to fibrosis or to atrophy of portions of the alimentary tract. In other words, it is thought that "the anæmia and the spinal cord changes are the results of a common cause" (Dr. Russel).

The cause which Dr. Russel and others assign is "some toxic state of the blood," the same toxin, in fact, as that which produces the pernicious anæmia. But if this be the only cause it is not easy to account for the occurrence of either anæmia without spinal sclerosis or of sclerosis without anæmia. Yet it is recognised that the sclerosis is not special to this particular disease, but may occur apart from it. It is, of course, possible that a toxin may be capricious in its selection of the organ or part of the organ to be attacked, for disease is not like a pigment which invariably stains the same tissues. But, on the whole, such erratic behaviour goes more against the toxin hypothesis than it does in favour of it. Dr. Lazarus, in referring to these spinal associations of pernicious anæmia, says that we are bound to assume the action of some common cause, but admits that the nature of this cause is a mystery.*

The view which is taken here is, of course, that the common factor by which these maladies are linked together is not a toxin. They may be chiefly or solely the expression of an inherent tendency on the part of certain organs to degenerate. They are instances of premature degeneration affecting two or more organs by correlation, aided, it may be, by the circumstance that the downfall of one gives rise to a debility which facilitates the downfall of the other. It must be regarded as in favour of this view that, according to Dr. Putnam,† fibrosis of the spinal cord associated with pernicious anæmia is especially prone to appear in enfeebled individuals who have passed middle age. He gives a number of cases in support of this opinion, and says that the degeneration is then usually very widespread.

Other associated diseases of great interest are those of *the bone marrow and bone*, connecting, as they do, the group of senilism of the blood organs with senilism of the skeleton. Dr. Goodhart has described an instance of the "interesting association of Hodgkin's disease of the spleen with osteitis deformans."‡ In 1861 Prof. Perrin reported a case which has every appearance of being a

* 'Nothnagel's Encyclopædia,' "Diseases of the Blood," p. 289.

† 'Journal of Nervous and Mental Diseases,' New York, 1891, vol. xvi, p. 69.

‡ 'Trans. Path. Soc.,' vol. xxxix, 1887-8, p. 262.

similar conjunction of Hodgkin's disease with osteomalacia. Both of these are referred to more fully in the next section.

Sometimes it is not the rarity of the associated disease nor the frequency of its occurrence, but its multiplicity which points to the presence of some common factor. Thus Talbot* gives details of the occurrence of chronic splenomegaly (splenic anæmia) in a male of fifty-nine who had also atrophic cirrhosis of the liver, chronic interstitial orchitis, advanced sclerosis of the aorta, moderate fibrosis of the pancreas and kidneys, fibroid lungs, and stunted growth. Nothing is said about the possibility of this conglomeration of diseases being the result of intoxication with alcohol or syphilis.

It would also be possible to quote instances of the association of Hodgkin's disease with chronic Bright's disease, pernicious anæmia with fibrous goitre, and other degenerations, but a sufficient number has not been collected to be of value as evidence.

There is one form of association which must now be referred to, and that is the occurrence of some form of idiopathic disease of the blood organs with *pre-natal or post-natal defects of development*. A good example of this association has been recorded by the late Dr. Carrington.† It is that of pernicious anæmia in conjunction with malposition of the left kidney, arrest of development of the left side of the uterus, and absence of the left ovary and Fallopian tube. It is true that this case is of old date and that no details of the anæmia are given, but occurring as it did in the experience of such a careful physician and expert pathologist as Dr. Carrington, it must be regarded as of some value. There was no evidence that the anæmia was secondary, and it was so severe as to destroy the patient.

In one of four recorded instances of pre-natal leukaemia (Dr. Pollman's)‡ there was a patent foramen ovale. In another (Sänger's)§ the mother died from chronic Bright's disease. In respect to the former case it may be objected that the abnormal state of the blood at birth was possibly the cause of the imperfection in the vascular system, but this, of course, is highly improbable.

The following was brought under our notice by the kindness of Dr. Abram :

The patient was born in 1894, and first seen by Dr. Abram in 1901, at the age of seven years. She was brought up as a girl because the external

* 'Degeneration.'

† 'Trans. Path. Soc.,' vol. xxxv, 1884, p. 237.

‡ 'Münch. med. Wochenschr.,' Bd. xxiv, 1898, S. 44.

§ 'Archiv f. Gynäk.,' 1888, Bd. xxxiii, S. 161.

genitals were distinctly feminine in appearance. But the child had a bass, masculine voice, the pelvis was narrow, the chest broad, and there appeared to be no true breast tissue, but nipples only. The bones were big and the muscles unusually prominent, giving a masculine contour to the body and limbs. There was a profusion of curly reddish hair on the head, and some on the pubes and axillæ, but none on the face. The nose and lower part of the face were well developed, so that the physiognomy was coarse and not in the least childish. She was very modest and did not like to be examined. Her height was 138·3 cm., and she measured 50·8 cm. round the abdomen, and 53·3 cm. round the chest. It seemed that she was large at birth, and that at the age of six months hair began to appear on the pubes. She never menstruated, but grew rapidly, and in a few years an alteration was noticed in the tone of the voice. It was thought that this was due to the presence of "adenoids" and to some enlargement of the tonsils. These were, in consequence, removed, but without the anticipated improvement. When Dr. Abram first saw the child he noticed that it was pale and sallow. In course of time this pallor increased, and the skin assumed a lemon colour. There was much debility, with shortness of breath, but no emaciation. An examination of the blood showed marked oligocythæmia and poikilocytosis. These rapidly increased, so that a few days before death, at the age of eight years, the erythrocytes were reduced to less than 1,000,000 per c.mm. There was no enlargement of the spleen or lymph-glands, but there were rickety nodes on the ribs, wrists and ankles. We saw this patient the day before death. No *post-mortem* examination was permitted. The case will be referred to again as an example of one form of sexual precocity (see p. 528).

Relations with Cancer.

A. The Red Blood : Pernicious Anæmia.

In regard to pernicious anæmia and its relations with either form of malignant disease we are prejudiced at the outset by the fact that when they occur together the most obvious explanation of the partnership is that the one is the direct cause of the other, and nearly always the anæmia is suspected to be the product of the cancer.

But in some instances the cancer is of such a size or character that it seems hardly possible for it to be the occasion of anæmia. It must then be looked upon either as a mere accidental concomitant, or as indicating some relation between the two of the same nature as that which exists between pernicious anæmia and degeneration of the nervous system, or of the stomach. Which of these views is correct it is impossible to say, but there is at any rate reasonable suspicion that the association is not a mere coincidence. For each case reported in which the pernicious anæmia precedes the cancer

there must be many which are not recorded, because the cancer comes first and is regarded as the *cause* of the anæmia. Moreover it is noteworthy that in those instances in which the anæmia seems to be prior to the cancer in order of sequence the stomach is the organ in which the malignancy is most often situated. Thus three cases are quoted by Lazarus* in which carcinomata of the stomach of very small size, and not ulcerating, were found after death in patients who had died with all the indications of pernicious anæmia. Even in respect to such cases as these last there is room for difference of opinion, for though it seems fairly clear that in these particular cases the anæmia must have been cryptogenetic, it was believed by Israel that, in a similar case examined by him, it was secondary, and due to concealed hæmorrhage. The subject is a difficult one to decide and the opinions of authorities are therefore somewhat contradictory. Thus Dr. Hunter says: "A sufficient number of cases have been recorded by competent observers to prove conclusively that all the characteristic features of pernicious anæmia may be presented by patients who are the subjects of malignant disease."† On the other hand, Professor Cabot gives his opinion that "the blood changes in malignant disease, so far as concerns the red cells, are those of secondary (*i. e.* not pernicious) anæmia."‡

Probably the right view to take of the relations between these diseases is to look upon them as sometimes associated by some bond of family relation; at other times as occurring together by mere chance; and at yet other times as having the same sort of causal link between them as that which exists between the *bothriocephalus* and pernicious anæmia.

B. The White Blood: Lymphadenoma; Splenic Anæmia.

When we turn from the association of cancer with pernicious anæmia, and inquire into the bearing that disease of the white-blood forming organs has on cancer, we see that there are some very important and suggestive gaps in their pathology. Thus, while

* 'Nothnagel's Encyclopædia,' "Diseases of the Blood," English translation, p. 243.

† In support of this statement see a case described by Dr. Houston ('Brit. Med. Journ.,' 1903, vol. ii, p. 185), also some collected by Dr. O. Knorpjuweit ('Deutsch. Arch. f. klin. Med.,' Bd. lxxvii, Heft 5 u. 6, S. 552), who sums up the records of thirteen cases.

‡ 'Diseases of the Blood,' p. 376.

apparently every structure of the body is liable to undergo malignant degeneration of its cells, primary cancer of the blood itself is not described in the text-books, and the same may be said of primary sarcoma of the spleen.* Such an omission as this is surpassingly strange, for who would anticipate that these two organs in particular would be exempt from malignant degeneration? They are cellular organs, are prone to undergo changes of growth and development, and ought, therefore, if analogy be of any significance, to be liable to the unicellular degeneration of cancer. And being of mesoblastic origin, the form that we should expect that cancer to assume would be sarcomatous. It is true that one kind of cancer is recognised, for the spleen, as well as the bone-marrow and lymph-glands, may be the seat of endotheliomata; yet, at the same time, it is apparently a fact that the existence of primary malignant transformation of the special or lymphoid cells of the spleen, or of the blood itself, is not regarded as established by the writers of text-books of medicine.

An explanation of this discrepancy is to be found by looking upon the lymph-glands as analogous to the spleen, and by taking the pathology of the former for our pattern in dealing with the spleen.

Two forms of true primary *cancerous transformation of lymph-glands* are now recognised by most writers, one being *endothelioma*, or cancer of the endothelial linings, and the other *sarcoma*, or cancer of the specific cells. And this latter—lympho-sarcoma—is usually regarded simply as a more virulent and acute form of “lymphadenoma.” It is generally believed that the two diseases cannot be separated. It is also held by some authorities that Hodgkin’s disease† and primary splenomegaly with anæmia are closely related, and that as the latter disease is termed “splenic anæmia,” so Hodgkin’s disease might, quite as properly, be termed “lymphatic anæmia” (Sir S. Wilks). But if this be right we have good reason to infer that just as lymphadenoma and lympho-sarcoma run into each other by imperceptible gradations, so there must be a corresponding lymphadenoma and lympho-sarcoma of the spleen—these two being different phases of the same process. We should then have primary degeneration of the lymph-glands and of the spleen as *organs* (lymphadenoma, splenic anæmia) and primary degeneration of their individual *cells*

* Weichselbaum (‘Virchow’s Archiv,’ vol. xxxv, 1881, p. 563) says that no satisfactory instance of primary sarcoma of the spleen has yet been recorded.

† By Hodgkin’s disease is meant that form of blood disease which is distinguished by primary degeneration of the lymph glands or lympharia without leukaemia.

(endothelioma, sarcoma). Just as lymph-gland sarcoma is distinguished by its rapid course, by its destructive and aggressive characters, so also ought we to recognise primary splenic sarcoma by similar rapidity of growth, by its defacing effects on splenic structure, and by the way it bursts the capsule, or, by means of the blood, invades distant parts. Such a view as this is exactly in keeping with all that we know of the relations of cells to organs, and of the differences between degenerations of organs and degenerations starting in cells or cell groups; for it necessarily follows that the differences between them will tend to disappear as organs become more simple in organisation. Thus, for example, the liver is a much specialised organ, and therefore the simple cells of a diffuse sarcomatosis occurring in its midst will be displayed in sharp contrast with the highly differentiated secretory cells. No one indeed could possibly mistake the one tissue for the other. On the other hand, if we imagine a similar sarcomatosis diffusing itself among the very primitive cells of the spleen, it would not be so easy to pick out the sarcoma cells from the normal cells.

Then, again, we have seen that cancer-cells exert a degenerating influence on the normal cells of the tissue or organ in which they lie, and this influence seems to be the more effectual the nearer the normal tissue approaches the malignant tissue in its development. Hence it is unlikely that a sarcoma appearing for the first time in a spleen will always stand out as a nodule or as nodules, but will sometimes be evenly distributed through its substance in the form of a sarcomatosis, corrupting all its cells, and presenting an appearance indistinguishable from that of an acute splenomegaly. Moreover this action is more or less reciprocal, so that the cancer will itself be modified by the normal and nearly related cells among which it permeates, and so again lead to the same result.

Normally lymphoid structure approaches that of a malignant degeneration. This is particularly the case with the lymph-glands of Hodgkin's disease and with the spleen of splenic anæmia. Thus Dr. Andrews* points out that the histology of the lymph-glands in Hodgkin's disease consists essentially in a simplification of structure, so that the distinction between cortex and medulla is lost, and the gland-tissue becomes more homogeneous. There is also more or less hyperplasia of the framework of connective tissue and of endothelial cells. These changes vary greatly. In one case there is very little increase of fibrous tissue and of endothelial cells, the gland being

* 'Lancet,' 1901, vol. ii, p. 1585.

soft and cellular; in another the fibrous and endothelial transformation may be so extreme that the glands are as uniformly tough and hard as fibromata.*

On the other hand, Miss Dorothy Reed,† as the result of her very complete investigations into the histology of the glands of Hodgkin's disease, arrives at the conclusion that there is a radical difference between lympho-sarcoma and lymph-adenoma.

These somewhat conflicting views on the subject of these disorders of the lymph-glands are not necessarily antagonistic, but are capable of being reconciled. We recognise clinically a less acute and less malignant disease tending to diffuse itself throughout most of the lymph-gland systems of the body, which we term "Hodgkin's disease," or to which we give the less satisfactory name of "lymph-adenoma." At the other extreme is a more severe disease, running a shorter course, and, though diffuse, tending to be more local in its manifestations. This is lympho-sarcoma. Midway between these two extremes there may be a morbid condition fitting in equally well with either of them, both clinically and morphologically, which we do equally right to call by the one name or the other. It is intermediate, and corresponds with the similar intermediate growths which spring from granulation-tissue (see p. 204).

If we now consider the changes which take place in the spleen of *splenic anemia* we shall find that they are after the same pattern. They also consist of simplification of tissue with fibrous or endothelial proliferation. The character and quantity of these changes vary as widely as they do in the lymph-glands of Hodgkin's disease. Sometimes the general fibrosis is so extreme that the Malpighian bodies are completely destroyed, and are fused into the interlacing bundles of fibrous tissue; at others the change is chiefly in the endothelial elements, simulating an endothelioma or carcinoma. In the latter event the proliferated endothelial cells may, according to

* We have ourselves made an autopsy on a patient (of Dr. Carling's) who died from chronic Hodgkin's disease and whose organs presented this fibrous degeneration to a most conspicuous degree. There seemed to be universal enlargement of the lymph-glands; and they were apparently without exception almost entirely fibrous. Those in the mediastinum were inseparably connected with thick bands of fibrous tissue, which ramified through the lungs in all directions, binding them down to the adherent pleura, causing much puckering, and usurping the place of normal lung tissue to such an extent that it was amazing that life had been able to continue so long as it had. Some of this fibrosis was apparently due to an added tubercular infection, for there were a few old caseous areas present, though the facts that these were so scanty, were not present at the apices, and that there had been no expectoration nor coughing, showed that they were secondary to the Hodgkin's disease.

† 'Johns Hopkins Hosp. Reports,' vol. x, 1902, p. 133.

Senator,* be carried from the spleen to the liver, thus fulfilling one of the chief requirements of true malignancy, namely metastasis. At other times the endothelial cells become transformed into fibrous tissue, and so add to the general fibrosis. Sometimes the change seems to start at the capsule and work in, at others the proliferation of the splenic cells is the main feature.

In short, with the exception, perhaps, of the nervous element, there seems to be no tissue either in the lymph-glands or spleen which may not be the starting-point or give the dominating note to the disease; and the result is under no circumstances a mere functional, consistent overgrowth having a definite object, such as would constitute "hypertrophy" or inflammation, but is an insane overgrowth of one or more tissues so that they preponderate over the rest. It is ill regulated, has no apparent object, and in all its characters reminds one rather of an endothelioma or of a sarcoma than of a physiological process.

In regard to the lymph-glands, again, though diffuse sarcomatosis is the rule, on rare occasions the sarcomatous or endotheliomatous degeneration focuses itself in some particular glands, the glands as a whole showing very little tendency to diffuse the morbid process through their structure. These are the unmistakable lympho-sarcomas. So also with the spleen. Primary sarcomata of the spleen do occasionally occur and remain localised in the splenic tissue and adjacent lymph-glands. Dr. Adolph,† who describes such a case, and discusses nineteen more, says he agrees with Grohé‡ and Max Borst in classifying primary lympho-sarcomata into two forms—(1) generalised lympho-sarcomata, and (2) lympho-sarcoma of the spleen or of lymph-glands with metastases in other lymph-glands.

Leukæmia.

The trend of opinion is apparently in the direction of regarding leukæmia and its allies as neoplastic or as having affinities with the neoplasms. Warthin,§ in a paper on "The Neoplasm Theory of Leukæmia," says that leukæmia must be regarded as a "neoplastic hyperplasia of the parent cells of the blood-cells," and gives details of two cases in support of his view, one of these being an instance of chloroma and the other of primary lympho-sarcoma of the ilium

* 'Lancet,' 1903, vol. ii, p. 402.

† 'Berlin. Klinik,' 1905, Heft 202, S. 1.

‡ Grohé, 'Virchow's Archives,' Bd. cl, 1897, S. 324.

§ 'Trans. Assoc. American Physicians,' vol. xix, 1904, p. 421.

with atypical lymphocytic leukaemia. Combined with this latter, it is interesting to note, was parenchymatous degeneration of the kidneys and of the liver.

Von Limbeck,* after discussing the pathology of leukaemia, comes to the conclusion that "we are now almost reduced to the conception of leukaemia as a process analogous to the malignant neoplasms."

Kundrat and also Banti† regard leukaemia as a form of sarcomatosis. As evidence of this Banti points to the atypical nature of the primary growth, of the secondary foci, and of the cells circulating in the blood, also to the involvement of the walls of the blood-vessels, of the capsules of lymph-glands, and of the periosteum. Of the same significance are the destruction of the endothelium, the occurrence of metastases (in the formation of which the cells of the organs affected take no part). Moreover, the hyperplasia of the bone-marrow may cause thickening or rarefaction of bone tissue similar to that which occurs in cancers of bone. Banti, after referring to these points, goes on to show that in some instances of sarcoma starting elsewhere than in the lymphatic system the blood becomes involved secondarily, and that under such circumstances an excess of mononuclear cells looking like lymphocytes is a conspicuous feature.

He also says that between typical leukaemia and typical sarcoma there are all kinds of intermediate forms.

Instances of sarcomas starting in tissues other than lymphatic and giving rise to leukaemia are also quoted by Drs. Martin and Mathewson.‡

Dr. Pincus§ says that in some cases the original sarcoma was of the spindle-cell variety.

Borderland cases are also furnished by *Chloroma*. Virchow, among others, believed this to be a sarcoma. Recklinghausen|| and Byrom Bramwell insist upon its intimate relations with leukaemia. Dock and Warthin¶ regard it "as a more malignant form of leukaemia," and Waldstein** classes it with the lymphomata.

The difficulty that may be experienced in the separation of the

* 'Pathology of the Blood,' p. 283, New Sydenham Soc. Transl.

† 'Riv. Crit. di clin. med. Firenze,' 1904, vol. iv, p. 785; see also 'Medical Chronicle,' 1904, p. 121.

‡ 'Brit. Med. Journ.,' 1896, vol. ii, p. 1634.

§ 'Nothnagel's Encyclopædia,' English ed., "Diseases of the Blood," p. 591

| 'Allgemeine Pathologie,' 1883, p. 440.

¶ 'Trans. Assoc. American Physicians,' vol. xix, 1904, p. 64.

** 'Virchow's Archives,' Bd. xci, 1883, S. 12.

different varieties of blood disease from one another is also well illustrated by the history of splenic anæmia and of Banti's disease, some cases of which were at one time thought to be carcinomata of the spleen, at others endotheliomata, and all were finally regarded as non-malignant and as varieties of splenic anæmia.

An interesting borderland case has also been described by Israel and Leyden.* This, in their opinion, showed the characteristic features of splenic leukæmia, of pernicious anæmia, and of multiple sarcomatosis all mixed together. Despite the eminence of these authorities this case cannot be regarded as of any great value, because it was recorded before the differential stains of Ehrlich had come into general use. It is now believed to be an instance of leukanæmia.

Another disease which is by some regarded as a sarcoma and by others as a form of non-malignant lymphoid enlargement is *mycosis fungoides*. It seems to be either allied to Hodgkin's disease or is a granulation-tissue sarcoma (see p. 203).

To sum up this subject of the relations of the blood disease group to malignance we seem justified in concluding that—

(1) *Endothelioma* may occur in the lymph-glands, spleen, bone-marrow or any other lymphoid structure. Endothelial proliferation, with the formation of giant-cells and their dissemination to different organs, are also features of some examples of Hodgkin's disease, of splenic anæmia, and even of leukæmia.† Some cases of splenic enlargement are at one time regarded as endotheliomatous, at others as manifestations of splenic anæmia. There are all possible gradations between endotheliomata and those members of the group which are usually considered as non-malignant.

(2) *Sarcoma* occurs in the lymph-glands, spleen, marrow, etc., and is so intimately related to the respective leukæmias and anæmias that the two conditions often cannot be separated. Though it is probably right to regard a virulent, acute, localised form of disease as being of local or unicellular origin, yet the tissue affinity to this form of malignancy is so close that there is no natural boundary between such cases and those slow generalised forms of disease which affect lymph-organs as a whole. The disease is one which picks out sometimes one tissue and sometimes another; sometimes starts in single cells or cell groups, and at others occurs simultaneously throughout an entire organ. If it begin in cells it is, in

* 'Berlin. klin. Wochenschr.,' 1890, Bd. xxvii, p. 231.

† See lymphatic leukæmia associated with endothelioma of the lymph-nodes, referred to by Ewing, 'Clinical Pathology of the Blood,' 2nd edition, 1904, p. 239.

the first place, an endothelioma, or a cellular or fibrous sarcoma according to whether it starts in endothelial cells, in lymph-cells, or in connective cells respectively. If it affect entire organs from the beginning then we term it a "splenic," "lymphatic," or "myeloid" anæmia or leukæmia. Hence we have some instances of true lympho-sarcomata, and others of simple Hodgkin's disease, splenic anæmia or leukæmia on the one hand and primary splenic sarcoma on the other. But between these extremes is a group of cases of which it is not easy to speak positively. They may be either the one or the other, for they partake of the characters of both.

Changes in the Blood in Normal Old Age.

If the march of old age be accompanied by a widespread phagocytosis we may anticipate that not only will there be an excessive fibrosis of the organs, but the blood will also show a relative or actual lymphocytosis. This, moreover, corresponds with all that has been said on the subject of old age, for if old age be a return to an infantile or embryonic condition, we may expect that the lymphocytosis of early infancy will be repeated.

Miss Hart-Davis has very kindly made a careful investigation into this subject of the blood state in old age.

Twenty normal men and women of from seventy to ninety years were chosen for the investigation. It was found that the state of their blood varied greatly. In some cases no change could be detected. The erythrocytes varied from five to six millions, and there were a few poikilocytes in two instances, but no other abnormalities were found. The white counts varied from 8000 to 10,000 cells per c.mm., with a slightly high lymphocyte count of about 35 per cent. In some the polymorphs showed ill-staining, diffuse nuclei, which resembled forms intermediate between normal cells and myelocytes.

Generally speaking these results tend to show that whereas the blood is less likely than other organs to show senile changes, yet that senile changes do occasionally take place and are comparable with those which go on among organs. Though no definite conclusions can be drawn from such a small number of cases, yet on the whole they point to some deterioration among the higher leucocytes and to slight increase of lower or embryonic forms.

Two cases not included among the twenty were manifestly abnormal, and *post-mortem* examinations were made. An average of four counts in each case at some weeks' interval showed less than 1,000,000 reds and about 10,000 whites. Nucleated reds of all types were seen, megaloblasts increasing in the later counts. Myelocytes were about 10 per cent. and large lymphocytes 35 per cent., with 19 per cent. small forms. The spleen was not enlarged. The bone-marrow contained free iron and large phagocytic cells ingesting as many as half a dozen red blood-discs. The red marrow was but little increased in amount. These two cases must be regarded as examples of senile (hypoplastic) pernicious anæmia.

VI

SUMMARY AND CONCLUSIONS

THE disorders of growth and development of the blood-forming organs furnish excellent examples of major and minor variations. It is, however, not necessary to say anything on this subject in connection with many of these disorders, for their biological position is obvious, and they have already been sufficiently discussed. But this can hardly be said of the highly important subject of the blood *degenerations*. We shall, therefore, first shortly epitomise what has been said in regard to them, and then put in a few words respecting their pathology and position as variations.

I. Pernicious Anæmia.

The disease pernicious anæmia is a degeneration of the red-blood making organs. This is proved by the way in which its main clinical and structural characters fulfil the conditions formulated at the beginning of this book. These characters, common to all premature senile degenerations, may be summed up as follows:

Clinically, pernicious anæmia, as its names signify, is often *idiopathic* and is *progressive*, but *interrupted* in its course, *pernicious* in its effects, *lethal*, and *incurable*; *arsenic*, however, occasionally brings about some temporary improvement, and may possibly, as a rare event, even effect a cure.

Structurally, pernicious anæmia consists in a reduction of red-blood tissue to its primitive simplicity. The effect upon the *marrow* of this retracement to an embryonic condition is to produce an apparent reinvigoration, so that it becomes red and swollen, filling out the cavities in which it is enclosed. At the same time nucleated red cells once more appear in the *blood*, and some of these cells are large and oval—so primitive, in fact, that they may even resemble the cells normal to the amphibians.

Two varieties of pernicious anæmia can be distinguished, corresponding severally with hypertrophic and atrophic cirrhosis of the liver, and with the large white kidney and the granular contracted kidney.

(1) The one, which may be termed *degenerative hyperplasia*,

resembling the larger form of cirrhosis, occurs in earlier life, and is characterised by the much greater enlargement of the red marrow. It is a degeneration occurring at a time of life when growth is still vigorous.

(2) The other form, which tallies with atrophic cirrhosis of the liver, is distinguished by a lesser formative power. Hence, with similar reversion of the bone-marrow, there is apparently no increase in size; or the marrow may be actually shrivelled, when compared with the marrow of early adult life. In fine the embryonic condition of the blood may seemingly be the only structural sign of degeneration.

Out of this hypoplastic form two varieties can be separated.

A. The first occurs earlier in life, is termed *aplastic anæmia*, and is essentially a premature senility taking place in an organ in a state of infantilism.

B. The second form is the old age form, and is the result of degeneration occurring prematurely in an organ already normally on the down grade, and therefore with its cells not capable of great reproductive activity.

Pathologically pernicious anæmia owes its peculiar features to the fact that the reversion occurs in an organ which comes into more intimate relations with the phagocytes than any other organ in the body, the lymph organs alone excepted. In the course of the proliferation or expansion of the red marrow which occurs as a necessary consequence of its degeneration, quantities of nucleated erythrocytes are poured into the blood-stream. Here they at once come into contact with the phagocytic lymphocytes, whose office it is to break up and destroy all immature red cells which may chance to find their way into the blood. The situation is vicious in the extreme. On the one hand the degenerated marrow pours an incessant stream of inefficient, embryonic discs into the blood-vessels and awaiting their influx are the lymphocytes or their analogues in the spleen, unable to destroy them fast enough. Exactly the same thing happens when blood from one species of animal is injected into the veins of another species. In fact, to all intents and purposes this is precisely what does happen in pernicious anæmia. Dr. Woods Hutchinson has pointed out that phylogenetically, embryonic blood is equivalent to the blood of an inferior species. Any disease, therefore, which reverses the development of the red discs must necessarily bring about their destruction.

Two results naturally ensue from this destruction. The one is that there is great scarcity of red blood. In order to make the

best of the few mature discs that are formed a change takes place in their structure. Their surface is increased by subdivision so that they become small and misshapen (poikilocytosis), and each corpuscle is made to carry more hæmoglobin.

The other result is that all the organs concerned in the work of phagocytosis and of elimination of waste hæmoglobin from the broken-down embryonic corpuscles show the effect of over-work. The spleen becomes bigger, large lymphocytes are relatively more plentiful, and there is an increase in the pigmentation of the liver, spleen, kidneys, skin, fæces and urine.

From a **biological** standpoint pernicious anæmia presents itself in two aspects, namely, (1) as a major and (2) as a minor variation.

(1) *As a major variation.*—We recognise a form which is apparently independent of cause, cropping up sporadically, and showing no particular preference for either rich or poor, but attacking those who live easy lives, as well as those whose circumstances involve hardship and privation. As a rule unusually malignant, it runs a rapid course, and affects younger people than is the case with the other form. It is rarely hereditary, and when heredity exists it is usually of the transforming and family kind, that is to say, the disease pernicious anæmia is not handed down to the descendants, but a similar degeneration of some other organ, and the heredity is shown by the outcrop of the associated degeneration among brothers and sisters.

(2) *As a minor variation.*—Pernicious anæmia is sometimes in part the result of causes, and these causes are occasionally operative over some districts in preference to others. These causes are, as yet, not fully understood, but seem to consist, for the most part, in the toxins of syphilis, of the infective fevers, and perhaps of those which emanate from bacteria infecting the mouth and intestines. Lead and the toxin of yeast may possibly act in a similar capacity.

Pernicious anæmia of this second kind is never solely produced in either of these ways, but owes its existence in an even larger degree to the presence of an inherent predisposition. It is the presence of both these factors—cause and predisposition—together which is requisite for the appearance of pernicious anæmia as a minor variation. This form is never inherited, occurs at a later age, and is usually less malignant.

II. Leukæmia.

Leukæmia is a presenile degeneration of the white-blood making organs. Allowing for accidents of place and of use, the disease

corresponds in all fundamental respects with pernicious anæmia. This may be shown in the following *resumé*.

Clinically, leukæmia is, like pernicious anæmia, *idiopathic*, *progressive*, but *intermittent* in course, *pernicious* in its effects, and *incurable*. It occasionally undergoes temporary improvement as the result of *arsenic*.

Structurally, it consists in reduction of leucocytes to their elemental simplicity. This reversion involves greatly increased multiplication together with corresponding impairment, or loss, of function.

This too hasty multiplication of cells accounts for the enlargement of the spleen or bone-marrow, and for the increase of leucocytes in the blood. Judged by this anatomical standard it is possible to distinguish two kinds of leukæmia:

(1) Leukæmia with excessive enlargement of spleen and marrow (hyperplastic degeneration).

(2) Hypoplastic leukæmia, in which there is less proliferation. In rare cases a differential count of the leucocytes may serve as almost the only guide to the nature of the disease; at any rate this may be the most important criterion.

Pathologically, the excess of leucocytes in the blood, which is the dominating feature of leukæmia, is largely the result of defective phagocytosis. Among the leucocytes undergoing copious proliferation are those which do the work of phagocytes, and the same degeneration which is responsible for their increase in quantity is also responsible for a corresponding decrease in quality. Hence the phagocytic power of the lymphocytes in the blood and spleen is weakened just at a time when most work is demanded. They are quite unable to cope with the tremendous increase of work which is thrust upon them, and the blood-vessels consequently become filled with embryonic and inert leucocytes, unable to develop and capable only of undergoing molecular decay.

Biologically the two sorts of variations can readily be recognised in leukæmia.

In some cases leukæmia is a *major* or discontinuous variation. Though it is true it cannot be termed an hereditary disease, yet it is such a sensational departure from the normal routine, and, as a rule, seems so completely independent of environment, that it corresponds with discontinuous rather than with continuous variations.

In other cases the influence of causes can be traced, and the disease is consequently a *minor* or continuous variation. It is then less malignant and tends to occur later in life.

SECTION IV

The Skeletal Group

The Disorders of Post-Natal Growth and Development of the Skeleton

I

INTRODUCTION

The growth and developmental disorders of cartilage and bone are determined by their normal relations, which differ at different ages. In developing bone normal growth is so balanced by absorption that when growth becomes excessive there may be no increase in the quantity of material.

LIKE the leucocyte- or erythrocyte-forming organs, the assembly of tissues which constitutes the skeleton may either be regarded as one organ or as subdivided into many organs. Looked at from the former aspect the skeleton is a framework which serves the double purpose of mechanically supporting the soft structures and of protecting them from injury. But in accomplishing this end other demands require satisfaction. Differentiation of function leads to differentiation of structure: some parts never ossify, but remain cartilage throughout life; bones are cancellous here and compact there; long in one place, short in another. The requirements of locomotion lead to the formation of joints, and, in order that no space shall be lost, the hollows of the bones are utilised for the purpose of blood formation. Lesser modifications of structure are produced by place and age, some parts being subjected to more strain than other parts, and senescence in one bone setting in earlier than in another bone.

All these many modifications of form and use influence the disorders of growth and development to an extent which exactly corresponds with the degree of modification.

Those modifications with which we are more particularly concerned are shown in—

(1) The relations of cartilage to bone.

(2) The joints and joint areas.

(1) **Cartilage and bone.**—Cartilage is for the most part so subservient to bone that at the time of its greatest activity cartilage is no more than a trellis or scaffolding upon which the young and plastic bone can be supported until it is strong enough to stand by itself. During the earliest stages of their career cartilage at first predominates, then the two go hand in hand, and finally bone is the more important of the two.

The most active stage of progressive development of cartilage alone is during foetal life, and of both cartilage and bone together is in late infancy, just as the baby is beginning to pass on into the stage of childhood. These, therefore, are the usual ages for the disorders of growth to take place.

But bone having once been formed and the cartilage absorbed, the cartilage ceases to be a factor in development, except under two sets of circumstances. Firstly, islands of cartilage are prone to be left behind by the advancing epiphysial lines, and, like all such “rests,” to become the seat of tumours. Secondly, in certain places where nothing is required but a flexible stay or buffer, the cartilage remains cartilage, settling down into the most passive and inert of all bodily structures. Adult cartilage is, indeed, so purely mechanical that its function could almost as well be performed by pieces of whalebone or of rubber inserted in its place. It is, therefore, the least likely of all tissues to undergo disorder of development. On the other hand, bone, though it serves a mechanical purpose, is still capable, if need be, of lighting up into activity. Under the stimulus of injury its cells proliferate abundantly to form new bone, or they may make a fairly good imitation of a joint. Corresponding with these physiological differences we find that the premature degeneration of cartilage is of very little moment, whereas premature degeneration of bone is an important disease.

(2) **Joints and joint areas.**—The bones, ligaments, cartilages, synovial membranes, which together constitute the joints, form the hinge organs of the locomotive apparatus, and, as definite physiological areas having well-defined uses, are, in common with all other organs, subject to pathological changes of growth and development.

A joint comprises not only the mere surfaces covered with articular cartilage, but all that bone area which is widened out in

order to fit it for its particular purpose. A knee-joint, for example, does not consist merely in the cartilaginous ends of the shafts of a femur and of a tibia. On the contrary, segregation of structure is required to correspond with the segregation of function. The bone expands, enlarging the surfaces which come into contact, separating off the joint-organ from the skeletal organ, just as the hand is specialised from the upper limb, or the hinge from the door.

Hence we must include in the word "joint" all those expanded ends of bones which constitute the terminal epiphyses.

The development and growth disorders of the joint areas occur during the progressive periods of joint development, that is, during the time when the epiphysis is active, for as soon as the epiphysis has become welded to the shaft all progress is at an end. The joint area, in fact, has a long, uneventful middle age before senile changes supervene. Hence the disorders of progressive development occur in early life, and there is a wide interval before the degenerative disorders make their appearance.

One other peculiarity of skeletal development must be remembered in order properly to understand the disorders of growth and development of the skeletal organ, and this peculiarity is so important and so germane to this branch of our subject that it may almost be termed the key of the situation. Hitherto the words "undergrowth" and "under-development" have been so closely associated with decrease of size, as the word "overgrowth" has with increase, that if an organ be undergrown we immediately infer that it must necessarily be smaller, or, if overgrown, then bigger, than normal. But when we come to apply these terms to the skeleton we shall see that these relations of cause and consequence are by no means coincident. The reason for this peculiarity is of course to be found in the fact that the process of normal progressive bone development is not one of unmixed growth, but of mixed deposition and absorption. Anything, therefore, which retards growth or development need not necessarily cause smallness, nor anything which accelerates growth or development, increase of size, for a very little defect in the adjustment of the two processes of addition and subtraction will be enough to turn that which ought to be a plus quantity into a minus, or *vice versâ*. Furthermore, as these defects and excesses are never perfectly even, but are always attended with some inequality, however slight, it can hardly cause surprise if the extremes of growth and development of bone are not revealed by the quantitative changes met with in the corresponding disorders of other organs.

Until lately the different forms of primary affections of the skeleton occurring in early life have been much confused, and even now it cannot be said that we are able clearly to distinguish between them. The following list of these disorders may serve in some measure to indicate how far we have reached in differentiation :

(1) *Fragilitas ossium* : Distinguished by brittleness alone without bending or other deformity and without gross anatomical changes.

(2) *Cleido-cranial dysostosis* : Defective development of membrane bone.

(3) *Osteogenesis imperfecta* : Defective development of bone formed on a super-structure of cartilage.

(4) *Achondroplasia* : Pre-natal hyperplasia or metaplasia of bone-forming cartilage (joint areas).

(5) *Rickets* : Post-natal hyperplasia of joint areas.

(6) *Osteomalacia* : Premature senile degeneration affecting the bone-marrow.

(7) *Osteitis deformans* : Premature senile degeneration of the bone-shaft.

(8) *Arthritis deformans* : Premature senile degeneration of joints.

Of these different diseases osteogenesis imperfecta, achondroplasia, and cleido-cranial dysostosis are pre-natal affections, and therefore do not, properly speaking, enter within the scope of this work ; but for the sake of completeness a short account of them will be given. *Fragilitas ossium* and *osteogenesis imperfecta* may be considered together, for, in all probability, they belong to the same class of disorder.

They can be classified as follows :

Overgrowth, or Simple Hyperplasia.

(1) Pre-natal (major variation)—achondroplasia hyperplastica.

(2) Post-natal (minor variation)—rickets.

Undergrowth, or Simple Hypoplasia.

Achondroplasia hypoplastica.

Infantilism, or Defective Development.

(1) Of membrane bone—cleido-cranial dysostosis.

(2) Of cartilage bone—osteogenesis imperfecta.

Senilism, or Premature Senile Degeneration.

(1) Of marrow—osteomalacia.

(2) Of bone—osteitis deformans.

(3) Of joints—arthritis deformans.

II

THE DISORDERS OF GROWTH OF THE SKELETON— OVERGROWTH

Overgrowth as a minor variation is rickets. Rickets is partly the result of causes ; occurs at a time of life when normal growth is becoming most vigorous, and is characterised by excessive activity of the proliferating “hypertrophic zone” of the terminal cartilage, and of the corresponding layer of periosteum. The muscles become weak from correlated atrophy, and other organs are also deranged secondarily. **Overgrowth as a major variation** is achondroplasia. Under this name are included three degrees of proliferative activity, to wit, achondroplasia hypoplastica, achondroplasia hyperplastica, and achondroplasia malica. The difference between achondroplasia and rickets can be accounted for by the earlier age at which achondroplasia occurs.

I. Overgrowth as a Minor Variation : Rickets.

WE have seen how overgrowth of the blood in chlorosis causes widespread disturbances of the body, and how these secondary disturbances have been mistaken for the prime factors in the disease.

So also is it with rickets. There is a tendency to look upon rickets as a general disease or toxæmia in the first place, and upon the bone changes as secondary. But so far this opinion is based solely upon theoretical considerations, for no specific bacterium or toxin has ever been discovered. On the other hand “Kanowitz, the leading authority on the anatomy of rickets, regards the hyperæmia of the periosteum, the marrow, the cartilage, and of the bone itself as the primary lesion, out of which all the others arise.”*

This, of course, does not dispose of the subject, but evidently we are not as yet justified in wandering outside the bare facts for any explanation of the pathology of rickets. And above all must we beware of the easy plausibility of the popular auto-intoxication hypothesis. So far all that we can see is that rickets is preceded by certain errors of diet and of hygiene in general, and is manifested by local disorders of the skeleton, and by other less definite derangements of the muscular, hæmic, and nervous systems. These different

* Professor Osler, ‘Principles and Practice of Medicine,’ 6th edition, p. 426.

manifestations of disease can be reconciled without dragging in the aid of an unknown toxin.

Like chlorosis, rickets is due to poor hygienic surroundings, but is especially the result of food containing excess of starch or deficiency of fat, though the stale air of slum dwellings, absence of sunlight, overcrowding and dirt in general are important contributory factors. Like chlorosis, too, the disease occurs sometimes without obvious cause in the children of well-to-do parents brought up after the most approved models. There is, indeed, reason to believe that rickets is not solely the product of outward circumstances, but is in part the result of inherent tendencies, though there is, as yet, no proof that these are hereditary. "External conditions of defective hygiene must therefore be regarded as influential but not essential" (Drs. Cheadle and Poynton). In other words, the disease, though a minor variation, and sometimes due more to circumstances than to inborn proclivities, may occasionally show very little trace of the former, and be due almost solely to the latter.

In the age of its onset also rickets may be compared with chlorosis and with the overgrowths of other organs, for it makes its appearance at a time of life when the joints are approaching the zenith of their growth, and are almost ready for use in crawling, standing, walking, or for purposes of prehension. Its favourite age is between three months and three years, though it may occur earlier or later. As "fœtal rickets," "rickets," and "late rickets" its incidence covers the whole of the time from the beginning of ossification in cartilage until its practical culmination at puberty.

Like chlorosis, rickets nearly always ends in recovery, and the deformities left behind are due to the locality of the overgrowth, and have nothing to do with the fundamental nature of the disease.

The skeletal disease is evidently an overgrowth or too hasty production of epiphysial and of periosteal bone, leading to impairment of function. The undue pressure of the proliferating cartilage cells jammed between the shaft and the epiphysis acts as such pressure does elsewhere. It "exaggerates the normal processes of absorption, so that the relation between removal and deposition is disturbed, absorption taking place too readily."*

Rickets consists in undue growth of that part of the epiphysial cartilage which is already enlarging for the purpose of bone formation. This, the so-called "hypertrophic zone," swells out as the result of the extraordinary proliferation of its cells, and by so doing encroaches upon the adjacent zone of provisional calcification. At

* *Ibid.*

the same time the arrangement of cartilage cells into columns is disordered, the groups being much less regularly arranged, and their cells varying widely in size, number, and in the characters and number of their nuclei. In short, as in the case of overgrowth of other organs, the growth is not merely excessive, but is also of an inferior order, so that the bone which results from it suffers in quality. Meanwhile similar overgrowth is going on in the periosteum, leading also to the deposit of a softer and somewhat poorer quality of bone. The disease might, in fact, with equal propriety be termed an overgrowth of bone as of joint areas, and it is only the special importance of the ends of the long bones which gives the changes of those parts so much greater prominence. Under normal circumstances the process of epiphysial bone formation consists in the multiplication of cartilage cells, the simultaneous absorption and calcification of the cartilaginous matrix, the continued absorption of this calcified material, and the formation of true osseous trabeculae by cartilage cells, now transformed into bone-cells. It is pretty evident that the success of this process of deposition and absorption must, to a large extent, depend upon the proper adjustment of each particular detail, and that any undue increase or decrease of a part of the scheme will derange the whole. Hence it can readily be understood that the exaggeration of the natural hyperplasia of cartilage cells, combined, as it is, with a certain amount of disorder, throws the whole process out of gear.

It is one of the elementary facts of pathology that pressure upon bone brings about its absorption. The pressure of an aneurysm upon the sternum or vertebræ leads to decalcification and excavation of these bones. The expansion of the bone-marrow by myelomata, osteomyelitis, pernicious anæmia or osteomalacia similarly first decalcifies and then attenuates the shafts of the long bones. The undue decalcification and absorption which take place in rickets can be accounted for in much the same way. The cells of the "hypertrophic zone," proliferating beyond their physiological limits, so push against the next zone as to hinder the process of calcification and hasten absorption.

Hence the very overgrowth which should accelerate deposition becomes itself the chief agent of waste, taking away with the one hand what it gives with the other. But laterally, where there is no bone to restrain the expansion of the cells, and the pressure is less, the "hypertrophic zone" bulges, giving rise to the nodes which are such a characteristic feature of rickets. The pressure produced by the overgrowth of periosteal cells is doubtless not so

great as that produced by the more pent up cells of the hypertrophic zone of the epiphyses, and absorption is consequently not so great. Hence the long bones of rickets diminish in length more than in thickness.

If this view of rickets be correct, it must necessarily follow that any disorder which hastens the growth of developing bone must facilitate the onset of rickets. Nothing seems better calculated to



FIG. 8.—*Extinct rickets*: Aged 13 years. The dwarfism is moderate, and is due to bending and shortening of the thigh and leg bones. There is knock-knee; the tibiae are sabre-shaped, the feet flat. The wrists and ankles are large. The thigh muscles are relatively big from defective adaptation to the shortened femora. (From 'Diagnosis,' published by J. Wright and Sons.)

produce this effect than sexual precocity, and it falls in with this conception of the nature of rickets that, according to Mr. Roger Williams* in his monograph on the subject, "a large proportion of these precocious children suffer from rachitis."

One result of the pressure of the overgrown hypertrophic zone and of corresponding cells of the periosteum is that the bone formed is deficient in calcareous matter. Hence it is liable to yield when

* 'Brit. Gynaecol. Journ.,' vol. xviii, 1902, p. '89.

pressure is put upon it. But the softness is not permanent; for the disease, having come to an end, is followed by a compensatory process. The bone scleroses and the shafts of the long bones become thickened with a deposit of dense hard bone, in bad cases leaving the individual warped, short, strong, and thick-set.

Conclusions.

Rickets may be regarded as an overgrowth of the skeletal organ, due in part to a derangement of metabolism proceeding mainly from irregularities of diet, and in part to inborn tendencies. In other words, rickets is a minor variation of the skeleton.

This overgrowth is manifested chiefly in the parts where normal growth is greatest, that is, at the growing ends of the long bones, rendering them liable to yield far too readily to pressure.

Closely associated with the skeleton are the muscles. These share in the morbid weakness of the skeleton, for they become wasted and flaccid, apparently in order that they may not damage the weakened bones by unduly powerful contractions. In this respect they behave as they do when a bone is broken, in sprains, or in disease of a joint. The muscles also become extremely sensitive, so as to protect the soft and pliable bones against rough handling.

Such widespread derangement of the skeletal and muscular structures within a short space of time can hardly take place without giving rise to some disturbance of the whole body. Hence the anæmia and splenic enlargement, and the sweating which so often accompany rickets; and hence, too, the diarrhœa, the peevishness, and other symptoms.

II. Overgrowth as a Major Variation: Achondroplasia.

The resemblance of achondroplasia to rickets is so close that they were for a time regarded as manifestations of the same morbid process. But recently pædologists have been so impressed by their points of difference that the two conditions are by most authorities now regarded as distinct diseases.

Possibly these views, based, the one on their manifest resemblances, and the other on their equally manifest differences, are both right. Rickets and achondroplasia may conceivably be the result of the same disease process acting upon the same part at different ages and to different degrees, much as hypertrophic cirrhosis of the liver resembles and differs from atrophic cirrhosis, or cretinism from myxœdema. In achondroplasia, as in rickets, the

brunt of the morbid process falls upon cartilage bone, particularly at the expanded ends, where growth is most active, and both are also characterised by "abnormal proliferation of cartilage with imperfect bone formation" (Klotz). But achondroplasia need not necessarily be due to overgrowth. It is quite in accordance with what has been said of the effect of undergrowth and overgrowth of this part upon bone formation, that either of these disorders may give rise to the phenomena which characterise that disease.

Indeed, according to Kaufmann,* who has described thirteen skeletons, there are three varieties of achondroplasia :

(1) Hypoplastica : The proliferation of cartilage cells is diminished and their columnar arrangement defective, though the epiphyses are of ordinary size.

(2) Hyperplastica : The proliferation of cartilage cells is excessive, but their columnar arrangement is defective and the epiphyses enlarged.

(3) Malica : The columnar arrangement is defective, the intracellular substance is gelatinous and vascular, and the cartilage is softened.

The structural characters are those of an infirmity of growth, accompanied by a mild degree of degeneration. The cartilage cells lose their orderly columnar arrangement, become variable in size and number and defective in function.

In achondroplasia the morbid process is more emphatic than in the overgrowth of rickets. Not only is there greater deformity of the epiphysial line but greater activity about the periosteum, so that bands of fibrous tissue advance between the epiphyses and the diaphyses, owing to the formation of the lower (fibrous) in preference to the higher (osseous) connective tissue. In short there is both more overgrowth and more degeneration in the hyperplasia of achondroplasia hyperplastica than in that of rickets.

A disorder of growth is necessarily most conspicuous wherever normal growth is most active. Overgrowth of cartilage is therefore most pronounced at the joint-epiphyses, the epiphyses of the various bony projections, such as the trochanters and tuberosities, being less implicated.

Kaufmann, as translated by Emerson,† shows that "the epiphysial cartilage activity, instead of limiting itself to one line of growth, becomes sluggish, or proceeds in all directions, and adds little to the length of the bone. The marrow-spaces invade the cartilage,

* 'Beitrag z. Path. Anat. und Allgem. Path. Jena,' 1893, Bd. xiii, S. 32.

† 'A System of Medicine,' by Osler and McCrae, vol. vi, p. 686.

and also the cortex of the shaft, producing a certain amount of osteoporosis intima. The periosteal bone formation is normal, or even unusually active, but has abnormally active bone absorption with which to contend. The vascularity of the marrow and of the epiphysial cartilage is remarkable."

Evidently the morbid process is fundamentally the same as in rickets, though it varies in detail.



FIG. 9.—*Achondroplasia hyperplastica*: Aged 14 years. 98 cm. high. The head is relatively large, the body long, the limbs short. The proximal segments of the limbs are more shortened than the distal. The ulna is more affected than the radius and the tibia than the fibula, so that the longer radius and fibula are bent. (From an article on "Dwarfism," in 'Diagnosis,' published by J. Wright and Sons.)

As we have already seen, the formation of bone is of such a nature that the greater the overgrowth the more likely is it to act as an impediment to bone formation. Hence in the disease under consideration the most conspicuous feature is the shortness of the bones.

But the same process of overgrowth occurring in a less degree in the periosteum leads to a greater deposit of bone under the periosteum than at the epiphysial lines. Hence the epiphyses are



FIG. 10.—*Achondroplasia hyperplastica*: From a skeleton in the Museum of the College of Surgeons, Edinburgh. The ribs are all shortened and so are the long bones of the limbs. There is shortening of the base of the skull, so that the skull is broad, and the bridge of the nose sunken. The joint areas are hyperplastic.

relatively wide and coarse, and the whole long bone is, considering its shortness, unnecessarily hard and thick.

All cartilage bones are affected in this unequal manner, but bones not passing through a cartilage stage are less implicated. Hence the parietal and frontal bones are well grown, and it is their disproportionate growth which accounts for the peculiar shape of the skull. Other chief characters of achondroplasia are the inward curve of the lower limbs, the large, coarse physiognomy, stunted, up-tilted nose, highly arched palate, contracted pelvis, and extreme lumbar lordosis. The hand is small, thick and square; the skull brachycephalic or rounded and pinched in at the base; the fingers short, pudgy, of almost equal length, and "trident shaped," the two outer and two inner fingers diverging at their second and third phalanges.

These features are the direct result of the overgrowth with its consequent inhibitory changes in the epiphysial cartilages on the one hand, and of continuance of growth of periosteal and membrane bone on the other. Moreover, the soft parts do not as a rule completely adapt themselves to the altered conditions, so that achondroplasias are noted for their comparatively big muscles and great strength, for their squat figures, and for a tendency to obesity. The skeleton as a whole is preternaturally thick and clumsy, and not only does the overgrowth give rise to disorders of this sort, but the bone laid down is not of the best quality. It is coarse, and is at first deficient in salts, so that it is liable to bend. These anatomical facts account for the characters of the disease. A disorder of growth of this description setting in between the third and sixth months of foetal life, when cartilage predominates in the skeleton, accounts for everything.

Achondroplasia as a Variation.

Our reasons for regarding achondroplasia as a major variation, and rickets as a minor variation of the skeletal organ, are chiefly as follows:

Achondroplasia affects the same skeletal tissues as rickets, and in a similar way, though to a greater degree.

Achondroplasia has no contemporary cause; rickets has many causes.

As is usual with major variations, achondroplasia occurs at an earlier age than rickets.

Achondroplasia is sometimes inherited, rickets never. Busch,*

* 'Neue Zeitschr. f. Geburtskunde,' 1836, Bd. iv, S. 110.

Apert,* Lepage,† Boeckh, Porak,‡ Osler§ have each recorded hereditary cases of achondroplasia. Another is recorded by W. F. Litchfield.|| Dr. Porter¶ has published an instance in which an octogenarian and his two sons were affected, and the father and the brother of the former were also said to be achondroplastic. Yet other cases are given by Dr. Emerson.** In one of them no less than five children were apparently affected. A well-marked and satisfactory example of the direct heredity of achondroplasia was recently to be seen in the exhibition of dwarfs called "Tiny Town" at Olympia. There was a striking facial and other resemblances between the two. The mother said that she had had two other children of small size and deformed, both of whom died at birth. It is believed that Dachshunds are the result of selective breeding of achondroplastic dogs. Sussex spaniels seem still more obviously of this nature.

Transforming heredity is fairly common. "Mr. Seligmann has pointed out that achondroplastic cows of the Dexter-Kerry breed are peculiarly apt to drop cretinous calves" (Dr. Poynton), and among human beings sporadic cretinism and achondroplasia may occur in different children of the same family. Dr. Hertoghe†† has also alluded to the co-existence in the same family of achondroplasia, obesity, rickets, myxœdema. Cavazzani‡‡ records a case of achondroplasia in a child whose mother was affected with Graves's disease; and Duranti,§§ one of a similar association in which the mother died of liver and renal disease.

Dr. Emerson, in his admirable article in Osler and McCrae's 'System of Medicine,' which has been freely drawn upon in the foregoing account, sums up the evidence for and against the relationship between rickets and achondroplasia. He points out (p. 687) that such authorities as Porak, Duranti, and Cestin believe that these diseases are akin. He himself thinks that "since the nature of neither rickets nor achondroplasia is understood, we are in no position to say whether or not they are related. They may be different manifestations of one and the same disease."

* "Une Famille d'Achondroplasiques," 'Soc. de Péd. de Paris,' February 16th, 1904.

† 'Revue d'Orthopédie,' 2^{me} S., tome vi, 1905, p. 109.

‡ 'Nouvel Arch. d'Obstét. et de Gyn.,' 1889.

§ 'Trans. Congr. Amer. Phys. and Surg.,' 1897, vol. iv, p. 190.

|| 'Austral. Med. Gaz.,' vol. xxvi, 1907, p. 624.

¶ 'Brit. Med. Journ.,' vol. i, 1907, p. 12.

** 'A System of Medicine,' Osler and McCrae, vol. vi, p. 684.

†† 'Nouvelles Recherches sur les Arrêts de Croissance et l'Infantilisme.'

‡‡ 'La Péd. Prat., Lille,' 1907, p. 125 (Emerson).

§§ 'Bull. de la Soc. Anat.,' 1900, p. 785 (Emerson).

III

DEVELOPMENTAL DISORDERS OF THE SKELETON: DEFECTIVE DEVELOPMENT OR INFANTILISM

Osteogenesis imperfecta is characterised by defective development of the bony skeleton, the bone material being calcified rather than ossified, and being in consequence abnormally brittle (*fragilitas ossium*). It is, as a rule, without known cause and is often hereditary, and is therefore a major variation. The affection sometimes terminates in premature degeneration (*osteomalacia* or *osteitis deformans*).

Cleido-cranial dysostosis is a similar defect of development of the membrane-formed skeleton.

Osteogenesis Imperfecta; Osteopsathyrosis.

UNDER the loose name of "*fragilitas ossium*" or "*osteopsathyrosis*" have been included a number of conditions which are now separated into distinct diseases and endowed with distinctive names. Nevertheless there is still much diversity of opinion as to the true nature of these affections and their relations one to the other. But it seems pretty clear that from among these disorders characterised by brittleness, one at least can be distinguished by certain well-marked peculiarities. This disease is *osteogenesis imperfecta*.

Osteogenesis imperfecta is a disease of late intra-uterine and early extra-uterine life and is often hereditary, the heredity being, as a rule, of the family kind. It is to all appearances invariably spontaneous in its origin.

Anatomically it is distinguished by defective development of both epiphysial and periosteal bone, the former being the more conspicuous of the two. The normal proliferation of cartilage cells and their transference into bone- and marrow-cells is interfered with, so that the cartilage capsules, instead of bursting, remain intact, and after undergoing calcification become incorporated in the shaft of the bone. Hence the bone which results is very imperfect. It is, for the most part, hardly true bone, for the process of bone formation being cut short at the stage of calcification, the result is little better than an imitation of bone. The trabeculae of the material so formed, instead of showing the usual

concentric arrangement of laminae, are either not laminated or are only slightly laminated. The bone-corpuscles do not pass beyond their undeveloped oval or rounded form, and do not continue their normal evolution into stellate cells.

It must not be forgotten that the periosteum of a long or short bone is but a later development of the perichondrium. So backward may be the process of bone development in some cases of osteogenesis imperfecta that these cartilage-producing properties may continue to be displayed by the periosteum of the shafts of the long bones at the period of birth,* or even later.

It will be gathered that as the processes of absorption are impaired, as well as those of deposition, the actual length of the long bones may not be materially altered. The disorder is a true defect of *development*, and its effect is therefore shown less in the quantity of the bone than in its quality. As in overgrowth (rickets, achondroplasia) the derangement is most conspicuous at the epiphyses, where development is normally most active, and is less notable in the shafts. Hence the skeleton does, as a rule, suffer to some extent in quantity, and the long bones of those affected with osteogenesis imperfecta are often shorter than the long bones of other members of their family at the same ages.

The changes in the periosteum correspond with those met with in the epiphyses. Dr. Hall Nichols,† from whom the above description is largely taken, says: "In this disease the periosteum forms separate plates of non-laminated or imperfectly laminated dense bone, in which are oval bone-cells and no Haversian canals. Instead of Haversian canals are large marrow-spaces. The trabeculae in the marrow canal are much less numerous than normal."

The marrow also shows the same blight of poor development, particularly near the epiphyses, where it is myxomatous or œdematous. So inherent and inveterate is the defective osteogenesis in the skeletal tissues that, according to Dr. Oskar Klotz,‡ when fractures occur the union is fibrous only, though the fibrous tissue may subsequently undergo calcification, but not ossification.

The membrane-formed bones of the skull are sometimes almost unaffected. At others they are so seriously implicated that hardly any bone exists, the brain receiving very little support, so that that part of the body resembles a shell-less egg. As a rule islets of bone

* "Osteogenesis Imperfecta," 'Journ. of Pathol. and Bacteriol.,' vol. xiii, 1909, p. 467.

† 'Keen's Surgery,' vol. ii, p. 51.

‡ *Ibid.*, p. 474.

occur here and there in the membranous calvarium. This malady is often associated with other developmental defects, such as spina bifida, club-foot, hare-lip.

The disproportionate deficiency in the osteogenesis of the cartilaginous base of the skull gives rise eventually to a sunken nose, a broad head, and a prominent forehead, similar to those in achondroplasia. Moreover, as in that disease, the soft tissues of the limbs are at first prone to be relatively redundant, so that in babies they form folds (Klotz), but as childhood is left behind and the natural relations between hard and soft tissues have opportunity to assert themselves this disproportion is to a large extent corrected.

Relations of Osteogenesis Imperfecta with Osteomalacia and Osteitis Deformans.

Many instances of undue brittleness of bones are caused by the presence of new growths, are the result of long disuse, or have some other known origin. But among them we find others which are dependent upon no ascertainable cause, but seem to arise spontaneously. Some of these last are characterised by extreme brittleness only, microscopical examination showing apparently no abnormality whatever,* though it seems highly improbable that such a very pronounced symptom should have no anatomical basis. In other cases, when a change of structure has been found, it has usually been an osteoporosis or rarification similar to that met with in the aged. But when the bone is not only brittle, but soft, so that it bends as well as breaks, there is reason to believe its condition approaches that of osteomalacia, the fact of bending being a sure sign of decalcification.† The bone of defective development has then undergone degeneration and fallen into a state of senilism.

A good instance of the osteomalacic degeneration of osteopsathyrosis is furnished by Mr. Clinton T. Dent.‡ In this case the disease first showed itself by fracture of a bone at the age of four months. Bending of several of the long bones then took place, and at the age of twenty-nine years, when the account was written, the case differed in no essential particular from one of osteomalacia. Numerous fractures had occurred, there was extreme softening with characteristic deformity, and the only distinction from osteomalacia of any consequence consisted in the shafts being smaller instead of

* Linck, 'Arch. f. Gynæc.,' vol. xxx, 1887, p. 264.

† "Idiopathic Osteopsathyrosis in Infancy and Childhood," Dr. Crozier Griffiths, 'Amer. Journ. Med. Sci.,' vol. exiii, 1897, p. 426.

‡ 'Trans. Med. Soc., Lond.,' vol. xx, 1897, p. 339.

bigger than usual. The skiagram which illustrates the paper shows that while the epiphysial ends of the long bones were very large, the diaphyses were even smaller than they are in health. This difference is to be accounted for by the age at which the disease began, for it occurred at a time of life when the ends of the long bones are very big in comparison with the shafts.

A similar case is recorded by Dr. Poynton* in an interesting paper on "Some Developmental Disorders in Childhood." There is a skiagram of the lower limbs, showing the tibia and fibula in a state of simple under-development, and the femora crumpled, thick, of irregular outline, deficient in bone salts, and, in one word, to all appearances osteomalacic.

This kind of bone-degeneration is comparable with those degenerations of the liver or kidney which supervene upon infantilism. These give rise to cirrhosis or to Bright's disease of the juvenile type, characterised by the comparative smallness of the organ, by its rapid course, and by the absence of ascertainable cause. Osteomalacia consecutive to osteogenesis imperfecta is, in fact, the *juvenile form* of that disease.

We have ourselves published† notes of a remarkable case of osteogenesis imperfecta occurring in association with other disorders of growth and development (Fig. 11).

The patient, a woman, aged 38 years, and undersized (1.44 m.) was born with a forward dislocation of the upper ends of both radii. Nine fractures occurred between the ages of six and thirty-six years, some of them from quite trifling causes. Thus she broke two ribs in the act of coughing, one of them snapping while we were engaged in binding up the other. At fifteen her legs became curved, as in the picture; a year afterwards an enormous tumour sprouted from the shaft of the left femur; and after an interval of twenty-one years, another of the size of an orange appeared on the upper end of the right femur.

It is now ten years since this account was written. No more fractures have taken place and the bones have remained much as they were. For many years there was so much pain and uneasiness at the projecting angle of the right tibia when she attempted to walk that at last we chiselled a wedge of bone from the tibia at the projection, bringing the right tibia into the same position as the left. So much callus was thrown out that it formed a conspicuous tumour round the fracture, causing the skin to become tense and shiny. This remained soft and continued gradually to increase for nearly three weeks, and then slowly contracted and hardened, but it did not

* 'Clinical Journal,' vol. xxx, 1907, p. 147.

† 'Lancet,' 1900, vol. i, p. 1866.

seem safe to let her bear any weight on the limb for quite two months after the operation. She has now, after nine months, a perceptible bulge of the bone about the fracture, but is devoid of pain, and the right leg is as strong as the left.

The wedge of bone removed was not soft, but was coarse and granular, and not differentiated into compact and cancellous tissue, and the medullary canal was so encroached upon as to be almost non-existent. The piece of



FIG. 11.—*Osteogenesis imperfecta*: Showing the bent leg bones, a large osteochondroma, and pre-natal dislocation of each radius.

bone was put on one side for further examination, but was unfortunately thrown away. Very little can therefore be gathered from the appearance of this piece of bone, seeing that it was removed from the site of an old fracture, and that its abnormal condition might in some respects be accounted for upon that score alone. Its coarse, almost mortary condition was, however, very different from the hard, dense texture which generally distinguishes old callus.

This patient was seen by Sir Jonathan Hutchinson and by Sir

James Paget. The latter thought the big tumour of the thigh was composed of bone and cartilage, an opinion in which Sir Jonathan concurred.

Sir Jonathan Hutchinson has very kindly sent us notes of a case under his care which bears a remarkable likeness to the one just described. The patient, who was a girl, aged $10\frac{1}{2}$ years, showed the following lesions, namely: (1) Fractures of the right forearm (three times), the left forearm (twice), of the right leg (three times), and of the right thigh (all these fractures united without leaving any very evident traces); (2) congenital dislocation of each radius accompanied by some defective development of the external condyle*; (3) bending of each ulna in its upper third and of each humerus; and (4) formation of tumours of the lower half of the right femur, and also of the middle of the left femur. The former subsequently disappeared, but the latter had not gone when the account was written.

The various lesions which characterise these two cases may be summed up under four headings, namely—(1) Pre-natal malformations; (2) fragility; (3) abnormal softness leading to bending; and (4) tumour formation. Now there can be no doubt that these two cases are examples of the same disease. It also seems certain that this common disease of which they are representative is closely related to osteomalacia and osteitis deformans. All three are distinguished by fragility of bones, by softening and bending, and by a tendency to be associated with the formation of tumours.

It would be by no means difficult to bring forward a series of cases to show that there is an unbroken connection between various kinds of primary idiopathic bone disease. *Osteogenesis imperfecta* might in this way be shown to merge on the one hand into *osteitis deformans*, and on the other into *osteomalacia*. *Osteitis deformans* would then merge into the “*non-calcifying plastic osteitis*” of Pitts and Shattock,† and into *osteomalacia*. *Osteomalacia* also passes on into the *multiple myelomata* and *myelomata*. Like the similar group of degenerations of the blood-forming organs, discussed in the last chapter, there are all sorts of intermediate forms, which weld the group together into a consistent whole. This group is connected with pre-natal disorders of development at the one end by the link

* Pre natal dislocation of the radius may occur in several different members of the same family (see Mr. F. B. Abbott's case, ‘Brit. Med. Journ.’ 1892, vol. i, p. 765) though the bones are straight. It must therefore be regarded as due to an error of pre-natal development, and not as the result of an accident at birth.

† ‘Trans. Path. Soc., Lond.,’ vol. xlviii, 1897, p. 176.

of osteogenesis imperfecta, and at the other end with normal premature senility by means of *senile osteoporosis* and *senile mollities*. Some good instances of these series of changes may be found in von Recklinghausen's contribution to Virchow's 'Festschrift.*' In one of his cases (aged 66 years) there were—(1) Bending of bones; (2) irregular thickening; and (3) formation of tumours, cystic, bony, and fibrous, among them being a spindle-shaped swelling of the upper part of the diaphysis of each femur. Though the anamnesis was very defective, von Recklinghausen considered the disease to be osteitis deformans of very long standing, commencing, indeed, in all probability within the first ten years of life. Hence the first onset of the osteitis deformans came within the age which is favoured by osteogenesis imperfecta. He alludes to a case recorded by Virchow of "diffuse deforming osteitis with tumours and cysts," and himself gives other cases of a similar nature. Some of these were allied rather to osteomalacia than to osteitis deformans. Thus in one, which occurred in a woman, aged 55 years, there was pronounced bone softening together with cystic growths. Von Recklinghausen himself considered it to be a case of modified osteomalacia. In another were cysts, numerous fractures, and a very thick calvarium. In yet another there was "fibrous osteitis," together with multiple sarcomata, and many fractures. His opinion was that in this last case the bone-softening was primary and the sarcomata secondary. He then mentions a case of a similar nature recorded by Hirschberg, which also was considered by that observer to be primarily one of osteomalacia, the disease being accompanied by cysts and sarcomata, and giving rise to fractures. Mr. John Langton† has also recorded an example of the association of idiopathic fragility of bones with the formation of a sarcoma.

The explanation of the relations between the several disorders that have been mentioned appears to be as follows: Osteogenesis imperfecta, being a defective development of bone, follows the rule that such defects, if of morbid degree, do not prolong life, but, on the contrary, hasten the onset of old age. In other words, any organ or tissue affected with infantilism is prone to premature degeneration or senilism. Hence osteogenesis imperfecta (infantilism) is liable to be followed by osteomalacia (senilism) or by osteitis deformans (senilism). These degenerations may exist in fairly

* "Die fibröse oder deformirende Ostitis, die Osteomalacie und der Osteoplastische Carcinom in ihren gegenseitigen Beziehungen," Virchow's 'Festschrift,' zu seinem lxxi. Geburtstage 1891.

† 'Trans. Clin. Soc., Lond.,' vol. xxix, 1896, p. 36.

characteristic form, or, it may be, in only mild degree. In either case the degeneration, affecting the entire skeletal organ, is peculiarly liable to lead on to tumour formation, in the same way that degeneration of other organs is liable to undergo the single cell overgrowths of adenomata, etc., or the degeneration of cancer, etc.

Such an explanation as this would account for the facts that in some of the radiograms of osteogenesis imperfecta a few of the long bones are obviously like those of osteomalacia or osteitis deformans, that the bones affected with the disease are prone to become the seats of tumours, and that descriptions of the histology of the bones are so variable. Thus the account by Dr. Hall Nichols already quoted is very different from that given by the late Professor Hamilton. Dr. Nichols is evidently describing a condition of defective development, whereas in the account by Professor Hamilton* it is equally evident that up to a certain point the minute anatomy is the same as that of osteitis deformans and of osteomalacia. Professor Hamilton, who quotes Langendorff and Mommsen, and gives two good plates, says that there is "dilatation of the Haversian canals, which are in part transformed into medullary spaces. The cement lines (von Ebner) which intervene and map out the borders of the Haversian systems have almost vanished. The borders of the trabeculae of bone stain red with carmine, probably owing to their being deprived of their calcic salts." The bone-marrow is red and hyperæmic, full of cells and poor in fat. It resembles fetal marrow (Virchow). Giant-cells are present in the dilated Haversian canals. Cyst-like cavities are also found. Parts of the trabeculae may be purely fibrous.

All this might be said of either osteitis deformans or of osteomalacia.

We can reconcile these discrepancies by supposing that Dr. Hall Nichols is describing true osteogenesis imperfecta, while Professor Hamilton is giving a description of the same disease after degeneration has set in.

Other discrepancies are possibly due to age incidence. Thus, Dr. Klotz points out that Kaufmann regards osteogenesis imperfecta as an improper production of cartilage in the first place, leading to an improper formation of bone; whereas in a case recorded by Dr. Klotz† the cartilage was well formed, nothing but the osteogenesis being at fault. It seems probable that this divergence of

* 'Text-book of Pathology,' vol. ii, Part 2, p. 837.

† 'Journ. of Pathol. and Bacteriol.' vol. xiii, 1909, p. 479.

opinion may have been due solely to the fact that the defect began earlier in the one case than in the other.

Paltauf* gives a short description of a case (Gottfried) of combined osteomalacia with delay of development of the skeleton. The pelvis of this patient is in the Pathological Anatomical Museum in Vienna (No. 2415). He was of the age of twenty-four years when he died from osteomalacia in 1852, and his height was 1.315 m. The extremities were short in comparison with the rest of the body, the head was large, the neck slender, and the spine, ribs, sternum and pelvis spongy, and devoid of compact substance, soft, and easily bent. Owing to the forward position of the sacral promontory the conjugate diameter of the pelvis was only 44 mm. The pelvic bones and the sacral and coccygeal vertebræ were united by cartilage. There was a cartilaginous lip, with beginnings of ossification, in the cristæ iliorum, and in the ischiæ and pubes. Attached to the pelvis were the lower four lumbar vertebræ and the upper thirds of the femora. The transverse and other processes contained cartilaginous patches, and isolated bone centres occurred in the epiphyses of the vertebræ. The three bone centres of the great trochanter were surrounded by cartilage. This may have been an instance of ateleiosis combined with osteomalacia, but it seems more probable that the osteomalacia was consecutive to the skeletal infantilism.

Defective Development of Membrane-formed Bone: Cleido=cranial Dysostosis.†

While osteogenesis imperfecta is a disorder of the development of bone-forming processes of the middle and later months of intra-uterine life, the disorder now under consideration appears to be a similar affection of the bone-forming processes of a still earlier date (second month).

It is strongly hereditary, and is characterised by an exaggeration of the transverse diameter of the skull, with retarded ossification of its sutures and fontanelles. Hence there is a median suture between the frontal and parietal bones; the face is small, the nose is shortened by imperfect formation of the nasal bones, and the floor of the orbit is retreating. The clavicle is usually reduced to a vestige at either end; dentition is delayed and imperfect.

* 'Ueber den Zwergwuchs,' S. 41.

† Marie et Sainton, 'Soc. Méd. des Hôpit. de Paris,' 1897, 3 sér., tome xiv, p. 706, et 1898, 3 sér., tome xv, p. 436; see also Jules Comby, 'Traité des Maladies de l'Enfant,' 2nd edition, 1904, p. 973.

The intelligence is unaffected. The disease is apt to be associated with the presence of other developmental disorders, such as club-foot, in other members of the family.

Probably defective development of the skeleton may occur at any stage of progressive development, though it is most common when normal osteogenesis is most active.

Dr. Looser has noticed osteogenesis imperfecta in a boy of fourteen, and terms it *O. tarda*. When it occurs later than this it probably merges by imperceptible degrees into normal deficiency of bone growth.

IV

PREMATURE SENILE DEGENERATION OR SENILISM OF THE SKELETON: OSTEOMALACIA; OSTEITIS DEFORMANS; ARTHRITIS DEFORMANS

The three components of the skeletal organ are the marrow, bone, and joint; and their presenile degenerations are severally termed "osteomalacia," "osteitis deformans," and "arthritis deformans." The *resemblance* between osteomalacia and osteitis deformans is very close, and indicates that they are fundamentally similar diseases. The *association* of these with other degenerations serves to link them with the degenerations of the blood organs (pernicious anæmia: Hodgkin's disease), kidneys (chronic Bright's disease), spinal cord (combined sclerosis), and with other developmental disorders. They have also very intimate relations with overgrowths and degenerations of cells (new growths and cancers). These seem often to arise out of the degenerated tissues much as cancer springs from the ichthyotic tongue, uterine myomata from the degenerated uterus, or adenomata from the degenerated thyroid or degenerated liver.

Introduction.

WE have seen that before ossification is completed the concentration of activity into the line of junction between shaft and epiphyses largely determines the character of the skeletal disorders of that period.

Ossification once finished, the errors of growth and progressive development need no longer be feared. The disorders to be apprehended are solely degenerative.

Moreover, we have no longer to take the epiphyses into consideration, for they have ceased to exist and have settled down into constituent parts of the joints, while most of the unossified cartilage still left is so inert that its degeneration is of academic interest only.

The skeleton may therefore be considered as consisting solely of three kinds of sub-organs, all at their highest degree of differentiation. These three component organs are the bone, the marrow, and the joints. Each is liable to undergo premature senile decay, and the names by which it is known are "osteitis deformans," "osteomalacia," and "arthritis deformans" respectively.

This statement is, however, too narrow, for the functions of the

normal bone medulla are, in the main, three. It is therefore liable to, not one, but three, different kinds of senilism. The chief use of the red marrow is to act as a manufactory of red blood-discs, and the most important disease is therefore a disease of the red-blood system, to wit, pernicious anæmia. The marrow stored in the cavities of the bones also acts as a manufactory of ordinary lymphoid tissue, and is on that account implicated in the degenerations of the leucocyte-forming organs, so that it undergoes changes in spleno-medullary leukæmia. But there is a third use of the red marrow. It is in intimate relation with the bone, in the meshes of which it lies, and helps to maintain its nutrition. It is consequently liable to attacks of degeneration from this point of vantage, the resultant disease being osteomalacia.

Just as the different forms of cirrhosis of the liver, of Bright's disease, of pernicious anæmia, and of leukæmia have been severally regarded as fundamentally distinct diseases, so also have osteitis deformans and osteomalacia. But nowadays there is a perceptible tendency to look upon them as so many groups, not of distinct diseases, but of closely allied forms of the same disease. Some of these groups have already been discussed, and reasons have been given for believing that the different members of the groups, and even the groups themselves, are more closely united than is usually supposed. Let us now adopt a similar method with osteomalacia and osteitis deformans, and it will, we think, be seen that they, too, are closely related—as closely, indeed, as the normal marrow is to the normal shaft.

Osteitis deformans and osteomalacia will now be taken together, their resemblances compared, their differences contrasted. We shall then deal with the subject of arthritis deformans separately.

The Resemblance between Osteitis Deformans and Osteomalacia.

This is no occasion to enter into the more intimate points of resemblance between osteomalacia and osteitis deformans. These will come out incidentally with sufficient force when we refer to other characters of the group. Even a casual glance reveals a remarkable resemblance between them. Both arise spontaneously, selecting some bones in preference to others. Both are fairly symmetrical, though they sometimes linger in one bone before proceeding to that of the opposite side or to other parts of the skeleton. Both are local diseases, and are distinguished by bending of bones and by fragility. In both there is decalcification and

deterioration of bone, and in both the deterioration takes place in the same direction, so that one of them (osteomalacia) has been named by Mr. Shattock "fibrous metaplasia of bone," and v. Recklinghausen has given to the other (osteitis deformans) the essentially similar name of "osteitis fibrosa."

Osteomalacia, especially when it affects only one bone, may be very difficult to distinguish from osteitis deformans. That there is more than a mere superficial resemblance between them is patent, for after he had termed his disease "osteitis deformans," Paget* found that he had been anticipated by Czerny, who had already given the same name to a case of osteomalacia of the tibia and fibula. It is highly improbable that two such acute observers should have pitched upon the same name unless there were facts of a similar nature in both diseases capable of a similar interpretation.

There is reason to believe that the two diseases may occur together in the same bone. Some of the instances of osteitis deformans and of osteomalacia reported in the medical journals present features characteristic of both diseases. One of these cases is described by Mr. J. R. Lunn,† who says of it that "from the microscopical appearance it appears to be a case of osteomalacia occurring in a single bone of an old man." (The patient was aged 86 years.) "On first examining the case it seemed to be one of senile atrophy with curvature." This specimen is preserved in the Hunterian Museum (No. 1241 e), and we have to thank the Council of the Royal College of Surgeons of England for permission to have it photographed (Fig. 12). It is put on the same shelf with specimens of osteitis deformans. In the description, which appears in the catalogue over the names of Mr. Lunn and Mr. Shattock, it is said: "This specimen appears to be allied to cases of osteitis deformans affecting only one bone." It will be noticed that there is very little thickening, except at the curve, but the bone has the coarse, gritty look of the bone of osteitis deformans, while, on the other hand, there is an aggressive growth of the marrow, causing absorption of the cancellous tissue at the upper end. The appearance of the tibia as a whole is certainly not characteristic of osteitis deformans, neither is it typical of osteomalacia, but it is equally true that in just those respects in which it differs in character from one disease it approaches that of the other. At one part the appearance is highly suggestive of osteomalacia, and at another is equally distinctive of osteitis deformans. If the bone were sawn in two at the

* 'Med.-Chir. Trans.,' 1884, vol. lxxv, p. 445.

† 'Path. Soc. Trans., Lond.,' vol. xxxvii, 1885, p. 266.

middle and the halves shown separately to one who did not know the specimen, he would not have much hesitation in saying that the upper half came from a patient with osteomalacia, and, in the



FIG. 12.—*Senilism of bone and marrow*: Section of humerus (on the right) showing changes characteristic of both osteitis deformans and osteomalacia: compared with section of healthy humerus (on the left). The diseased bone is thickened, lengthened and bent. In the upper half there is an aggressive growth of the marrow encroaching upon and thinning the shaft as in osteomalacia; the lower half is thick, coarse, and of uneven outline, like the bone of osteitis deformans. From the 'Lancet.'

absence of syphilis, he would be equally positive that the lower half was from a case of osteitis deformans.

When the membrane bones of the skull are affected with osteo-

malacia the appearance may closely resemble, or, indeed, be identical with, that produced by osteitis deformans. This is well shown in a specimen of osteomalacia of Dr. Goodhart's, preserved in Guy's Hospital Museum. The calvarium in this case is coarse, granular, devoid of diploë, and deeply scored by the trenches made by blood-vessels. The sutures are obliterated, and were the bone only a little thicker, it could not be distinguished from the skull-cap usually met with in osteitis deformans.

These are examples of the conjunction of the two diseases. There are other specimens (*e. g.* No. 387 University College Hospital Museum) in the London museums which appear to show a similar mixture.

Another connecting link between the two diseases is furnished by their common tendency to tumour formation. In osteomalacia this is best shown in that special variety which has received the name of "Kahler's disease"; and tumour formation is a well-known feature of osteitis deformans.

Structural Changes.

Osteomalacia is not solely a disease of the bone-marrow, but of both marrow and shaft.

The changes in the *marrow* vary greatly, according to the stage of the disease, the rapidity of its course, and other circumstances, but are, in the main, of two kinds. There is first proliferation, with other indications of retrogressive development of red marrow-cells, resulting in the formation of enormous quantities of embryonic marrow, and following rapidly upon this, or going on at the same time, is the second series of changes. These changes are molecular and destructive, and consist in the extravasation of blood and the formation of gelatinous deposits and other products of cell destruction. In advanced cases the marrow may consist of little more than a structureless jelly-like reddish pulp. In some extreme instances the molecular decay reaches to such a pitch that ultimately nothing is left but a thin gelatinous shell, or capsule, containing oil, into which the finger can be pushed with ease, leaving a hole for the escape of the contents. As a rule the anatomical changes are less extreme, and consist in the main of the formation of a large excess of thick, red or maroon-coloured marrow, enlarging and filling the cavity of the bone. But, however much appearances may vary, every case shows at some stage changes which indicate retrogression to an embryonic condition, and others indicative of molecular decay.

Different interpretations seem to have been put upon these alterations according to the stage at which they were seen. They are most characteristic at a comparatively early period.

The changes in the *shaft*, when looked at superficially, are very different, but are in reality of the same kind as those which appear in the marrow. They differ only in accordance with the difference in character of the tissue affected. The marrow, like the white-blood organs, is composed of cells which have undergone very little development. Hence, degeneration is expressed far more by proliferation and increase than by obvious alterations of the cells. But the shaft is composed of more highly organised cells, and degeneration is therefore expressed in a different way.

The marrow is, in one respect, like a pauper community. When affected by some widespread depression of trade all paupers seem to be impoverished alike. It can only be said of them that they were poor before, but afterwards they are poorer. But when there are wider class distinctions a similar depression will affect individuals more unequally, so that those who were rich become poor. In the shaft of a malacic bone there is simplification of the higher or more specialised bone-cells, beginning with disappearance of their characteristic processes. At the same time proliferation takes place of the lymphoid tissue which runs up the Haversian canals, and such retrograde changes in the Haversian systems as will ultimately reverse the order of their development, and bring the bone back to that cellular condition from which it started. This change is, of course, the work of those macrophages, the osteoclasts. The process of retrogression or degeneration is best seen on the outskirts of the diseased area, where the marrow touches the shaft of the bone. It first shows itself as decalcification. This is a vital and not a mechanical or chemical process, and is facilitated, or partly caused, by the pressure of the increasing marrow on the bone. It resembles, in fact, the decalcification which is produced by aneurysms when they impinge on bones, but is doubtless accelerated in these cases of osteomalacia because of the inherent tendency of the bone to degenerate. There seems no reason to doubt that the overgrowth of the marrow is, under the circumstances, amply sufficient to account for the decalcification, for it is not at all unusual to find the marrow in a malacic bone taking up more room than both marrow and bone together of the healthy bone. It has been noticed that in some cases, if not in all, the decalcified layers are not immediately absorbed, but after the removal of the bone-salts fuse together or split into fibres. The

bone, in short, reverses its development. It first goes back to the cartilage stage of its existence, or to something akin to it, then to the stage of fibrous tissue, next to the stage of primitive fibroblasts, and finally to the round indifferent cells from which the fibroblasts originated. These go to add to the mass of embryonic and decayed tissue which fills the bone-cavities.

In *osteitis deformans*, as in osteomalacia, the changes are not confined to one tissue, but are present in both marrow and shaft. Not only is this the case, but the changes in shaft and marrow are essentially similar in the two diseases, though they differ in detail. In *osteitis deformans* they are slower, and the degeneration does not continue to such an extreme degree. There are apparently two reasons for these differences. In the first place *compact bone* is a far more stable tissue than the cellular medulla. It is, therefore, much less impressionable to those influences which aggravate or ameliorate osteomalacia. Osteomalacia also occurs at an age which subjects it to the changes produced by menstruation and pregnancy, whereas *osteitis deformans* is a disease of later life, and on that account alone may reasonably be expected to take a more chronic course. We consequently find in *osteitis deformans* decalcification and absorption similar to that which forms such a conspicuous feature of osteomalacia, though they are modified by the peculiar circumstances of the tissue and age in which they occur. In *osteitis deformans* the decalcification and absorption are less pronounced. Although the lacunæ are eaten out and enlarged by the phagocytic osteoclasts, yet the denudation is slower and less complete than in osteomalacia. Moreover, there is a constructive process going on at the same time, for what is taken away with the one hand is put back with the other. But unfortunately this fresh bone is of poor quality. Good bone is, in fact, replaced by bad. The process is a deforming process and a degradation.*

To put it shortly—in *osteitis deformans* the bone is first reduced to its acalcic or precalcic stage of development; the Haversian systems become distorted, the bone-corpuscles returning to their primitive simplicity, and the canals filling with embryonic tissue. Calcification rather than ossification of this fibrous or gelatinous basis then takes place, and the “bone” is left in a coarse, porous,

* Mr. Lunn, in comparing *osteitis deformans* with osteomalacia, says, “The latter, which I think is equally general, consists in a process of osseous absorption, probably identical, but more severe, and there is no time for the mechanical rectification of the bones by compensating overgrowth. The diseases *osteitis deformans* and osteomalacia appear to be both constitutional diseases, and I think have a strong connection with each other.” (*Illustrated Medical News*, 1889, vol. ii, p. 183.)

granular condition, totally different from the well-organised compact tissue of normal bone. This change takes place, not centrifugally, as in osteomalacia, but interstitially, from the point of vantage, not of the marrow, but of the permeating Haversian canals.

While changes are going on in the shaft other changes are taking place in the *medulla*, and these also are of a similar nature to those which occur in osteomalacia. Proliferation of red marrow-cells is, as a rule, not nearly so marked in osteitis deformans, though it may be fairly conspicuous, as we have already seen.

There seems to be no essential difference between the structural changes in the two diseases when we consider that one is a more chronic malady of a comparatively inert tissue occurring in the old, while the other is a more active disease of the same nature, affecting a more mobile tissue at a younger age. In both there is simplification of the higher-class cells, with proliferation of the lower-class cells, and general retrogression to tissue of a more primitive kind. Hence, both maladies fall into line with the degeneration of the liver, kidneys, blood-forming and other organs.

A connecting link with the other groups is formed by arterial sclerosis, for the changes in a sclerosed artery are identical in principle with those which take place in the shaft of the bone in osteitis deformans. The artery, like the bone, is deformed, weakened, thickened, hardened, and lengthened by a fibrous hyperplasia of its walls. In both cases the change consists in a degradation of tissue from a more highly developed condition to a lower, and in both cases the disease is peculiar to old age, normal or premature.

Associations.

The bone degenerations are connected with the degenerations of the blood-forming organs through lymphadenia ossium and lymphadenomatosis of bones. These serve to connect the bone group with Hodgkin's disease. They are related, in a similar way, with pernicious anaemia, through those forms of mollities in which extreme marrow hyperplasia with decalcification and absorption co-exist with weakness, anaemia, a low blood-count, and poikilocytosis.*

In the first part of this book two instances were mentioned of the occurrence of lymphadenoma in association with osteitis deformans and with mollities ossium respectively. One of these was Dr. Goodhart's case of osteitis deformans occurring in association with lymph-

* Grawitz, 'Virch. Arch.,' vol. vi, 1879, S. 7; also Muir, 'Journal of Pathology,' vol. ii, 1894, p. 363.

adenoma.* The patient was a man, aged 65 years. There were "many fleshy tubera apparently of a cancerous nature in the loin, and several firm, fleshy, cancer-like glands in the mediastinum and abdomen. One or two small nodules of growth in the pleura." The spleen was full of large circumscribed yellow masses, looking like the hardbake spleen of Hodgkin's disease. Dr. Goodhart considered the case to be an example of the "interesting association of Hodgkin's disease of the spleen with osteitis deformans." The occurrence of osteomalacia and lymphadenoma in the same person was described in 1861 by Professor Perrin,† who calls it a general hypertrophy of the "whole of the ganglionic lymphatic system," with softening of the tissue of the bones. The age of the patient was sixty-eight years. His disease began with swelling of the axillary glands seven years before the account was written. The bones became unduly brittle (there were five fractures), and were so soft that they could be cut with a knife. As nothing is said of the presence of a primary tumour and the glandular enlargement was pronounced and widespread, there is reason to believe that the bone softening was due to true osteomalacia, and that the glandular swelling was also primary. It may have been an instance of multiple myelomata (Kahler's disease), but the statement that the disease began with enlargement of the axillary glands is suggestive of Hodgkin's disease. Drs. Fagge and Pye Smith‡ have stated that softness of bone is the "fundamental distinction" between osteomalacia and allied diseases.

Connecting links with the previous group of blood degenerations are furnished not only by those cases in which Hodgkin's disease and osteomalacia co-exist, but by the occurrence of pernicious anæmia or leukæmia in one member of a family and osteomalacia in another (reference lost). Dr. Parkes Weber§ sees a very intimate connection between the leukæmias and the multiple myelomas.

In glancing over the reports of cases of *osteitis deformans* it is again and again seen to be allied with some other degeneration or outgrowth, either in the same individual or in some other member of the family. Chronic Bright's disease, imbecility, optic atrophy, goitre, emphysema, carcinoma, sarcoma, molluscous growths, and tumours of fat and of cartilage are all mentioned in different cases. Special attention is called by some writers to certain of these asso-

* 'Path. Soc. Trans., Lond.,' vol. xxxix, 1898, p. 262.

† 'Bull. de la Soc. Anat.,' 1861, S. 2, p. 247.

‡ 'Principles and Practice of Medicine,' 1st edition, p. 575.

§ 'Med.-Chir. Trans.,' vol. lxxxvi, 1903, p. 430.

ciations, such as that with cancers, with bulbar paralysis, or with degeneration of the posterior columns of the spinal cord.

Tourette and Marinesco* describe osteitis deformans in which the posterior columns of the spinal cord were found to have undergone fibrous degeneration, and refer to an earlier case of Tourette's in which a similar lesion was found in the cervical region.

A good instance of the association of *osteomalacia* with other degenerations is published by Dr. George Docker,† who, in describing the osteomalacia of a woman, aged 24 years, says that the mother possessed a goitre as large as a man's head, and had suffered from "rheumatic" (osteocopic) pains of the limbs while she was carrying her first child. A brother had a pre-natal deformity of the right thumb, while the patient herself had a goitre and a cartilaginous tumour of the right femur, and was found after death to be affected with fibrous degeneration of the spleen, the kidneys and the ovaries.

In the reports of other cases of osteomalacia we find cleft palate, goitre, exophthalmic goitre, cataract, or chronic Bright's disease. In a list of twenty-eight cases of the myelomatous form of mollities collected by Dr. Parkes Weber,‡ there were no less than five cases of chronic Bright's disease. In one case (that of Lichtheim and Askanazy's) the disease was associated with lymphatic leukaemia; and in another (Kalischer's) one of the patient's daughters had died at the age of thirty from pernicious anaemia. One of Paget's original cases of osteitis deformans died from chronic Bright's disease.§

Among these associated disorders are degenerative affections of the central nervous system. These occur so often as to have led to the belief that osteomalacia may be directly produced by some trophic disturbance originating in the brain or cord. Dr. Wigglesworth|| examined sections of ribs from thirty insane individuals, and found that three of them (or 11 per cent.) were markedly abnormal. One was from a demented woman aged thirty-eight, one from a woman of seventy-eight with senile dementia, and the third from an epileptic imbecile of thirty-eight. In all three the condition of the bones was one of "senile osteoporosis" or "senile osteomalacia." It is right to say that Dr. Wigglesworth considers this disease to be quite distinct from ordinary osteomalacia.

An instance is also recorded of the occurrence in the same patient

* 'Nouvelle Iconographie de la Salpêtrière,' vol. viii, 1895, p. 205.

† 'Amer. Journ. Med. Sci.,' vol. cix, 1895, No. 5, p. 499.

‡ 'Med.-Chir. Trans.,' vol. lxxxvi, 1903, p. 395.

§ *Ibid.*, vol. lxxv, 1882, p. 227.

|| 'Brit. Med. Journ.,' 1883, vol. ii, p. 629.

of osteomalacia and hydromyelia, and another of osteomalacia with syringomyelia. The association of skeletal degeneration with degenerations of the nervous system is comparable with the similar association of degenerations of the kidney (chronic Bright's disease) and blood (leukæmia and pernicious anæmia). The one degeneration is both cause and consequence of the other, but probably the chief reason for their conjunction is the inherent "predisposition" of certain organs to degenerate together. If this be correct it is to be expected that of all organs the muscles would be most likely to show degenerative changes in osteomalacia and osteitis deformans, seeing that they come into such close physiological correlation with the bones. But we can find only one instance in which the association of definite muscular degeneration has been recorded, and this is given by Friedreich, who, on examining the muscles of a case of osteomalacia, "found histological appearances like those which occur in progressive muscular atrophy."* But this may not be the only case, for one of the most conspicuous symptoms of osteomalacia seems to be muscular weakness. It occurs so often and is sometimes so extreme that it has given rise to the suggestion that osteomalacia is a "trophoneurosis," not of the bones only, but of the muscles as well.

In a case recorded by Dr. Judson Bury† the osteomalacia was associated with premature general development. The child's limbs were bent at birth, though there were no traces of rickets. At its death, at the age of 8 months, the upper centre of ossification in one tibia was found to be very large, while the lower was already present and well formed, though it normally does not appear until the second year. The other bones were in a similar condition. The prematurity was, however, not sufficiently marked to be of much consequence. It may have been within the limits of normal variation.

Diseases of the group sometimes occur in connection with some anomaly of pre-natal development. Instances of this have been already given when referring to osteopsathyrosis. Another is provided by Dr. Docker,‡ who reports on a patient with osteomalacia who had pre-natal defects of the right thumb, the metacarpus and first phalanx being absent. There was also thyroid enlargement, and the mother had an enormous goitre.

* Drs. Fagge and Pye-Smith, 'Text-book of Medicine,' 4th edition, p. 546.

† 'Brit. Med. Journ.,' vol. i, 1884, p. 213.

‡ 'Amer. Journ. Med. Sci.,' 1895, vol. cix, p. 499.

Relations with Innocent and Malignant Tumours.

There is every reason to believe that the hyperplasia of *osteomalacia* may form a breeding-ground for new growths in the same way that the goitrous thyroid gland, the fibrous and degenerated breast, the ichtthyotic tongue, and, in rare cases, the cirrhotic liver may severally pave the way for malignant disease.

Much the same may also be said of *osteitis deformans*, for the bones in that disease are peculiarly liable to become the seat of cancerous tumours. This conjunction is, in part, to be explained on the ground that the tissues in general become more liable to single-cell degeneration as they increase in age. But in addition to this there is also an undoubted special proclivity of the hyperplastic bone itself. It has already advanced to a half-way stage, and the final descent into cancer is rendered thereby so much the easier.

The myelomata and sarcomata occur more frequently than the carcinomata, because the skeleton is mesoblastic. "The myelomata resemble osteomalacia both in clinical features and pathological products."* The myelomata seem to take up an intermediate position between osteomalacia and sarcomata, and difference of opinion has been expressed as to whether they should be regarded as adenomata or as sarcomata,† for while some behave like innocent tumours, others may, less often, show all the features of malignancy. This reminds one of the similar controversy in regard to the innocent or sarcomatous nature of the enlarged glands of Hodgkin's disease. The myelomata appear to be manifestations of degeneration in a more localised and concentrated form. Connecting links between the myelomata and osteomalacia are not infrequent. Their occurrence together is described by Hirschberg,‡ Butlin,§ and others.

Myelomata also occur with osteitis deformans. Thus Mr. B. Pitts and S. G. Shattock || gave details of a case under Mr. A. O. Mackellar's care, in which a growth, having all the characters of myeloid disease, occurred in a tibia affected with osteitis deformans.

It is not improbable that some of the heterologous tumours which are occasionally found in cases of osteitis deformans are not in

* 'Wilk's and Moxon's Pathological Anatomy,' 1875, p. 63.

† Wieland, 'Virchow's Archiv,' Bd. clxvi, Heft 1, 1901; Bradshaw, 'Lancet,' 1902, vol. ii, p. 929; Jochmann and Schumm, 'Zeitschr. f. klin. Med.,' 1902, Bd. xlv, S. 445.

‡ 'Centralblatt für Chirurgie'; see Recklinghausen in Virchow's 'Festschrift,' zu seinem, lxxi. Geburtstage 1891.

§ 'Path. Soc. Trans., Lond.,' vol. xxxi, 1880, p. 277.

|| *Ibid.*, vol. xxxvi, 1885, p. 184.

reality secondary to the disease, but occur only in association with it as the expression of a common morbid tendency. An instructive case which appears to support this view is reported by Mr. C. E. Richmond.* Spontaneous fracture of a femur had occurred in a patient who was affected with scirrhous of the breast and with growths which appeared to be secondary to it. On *post-mortem* examination cancers were found in the iliac crests and elsewhere. A section of one femur showed that that bone was not the seat of cancer, but that it had undergone changes characteristic of osteitis deformans. Here it seems probable that the cancer and the osteitis deformans were not immediately connected, but were the associated outcome of the same senile decrepitude. In this case the cancer of the breasts was to all appearances the first to show itself, the osteitis deformans coming next. There seems no reason why the order should not sometimes be reversed, and cancer appear, not as the result of the osteitis deformans, but as the result of correlation. The two would then occur together as associated errors of retrogressive development, much as a club foot and hare-lip may be associated errors of progressive development.

Kahler's Disease.

Some instances of myelomata occurring in malacic bones are no doubt examples of that special form of mollities which has been termed "Kahler's disease" or "myelopathic albumosuria" (Bradshaw). This disease, according to Bradshaw, shows a marked preference for males, occurs in the second half of life, and affects chiefly the vertebral column, ribs, and sternum.† The myelomata may consist of different sorts of neoplasm in different cases, but it is significant of their benign character that there are no metastatic growths in other tissues, except occasionally in adjacent lymph-glands. The disease is characterised by the presence of the Bence-Jones proteid in the urine.

All these facts tend to show that there are very intimate relations between the degenerations of the skeleton as an organ (osteomalacia, osteitis deformans) and of its individual cells (myeloma, sarcoma). They are prone to occur together and to simulate each other both in their clinical relations and in their structural characters. An explanation can be found for these relations if we regard the bone-

* 'Manchester Pathological Society,' February 13th, 1885.

† Dr. Parkes Weber, 'Med.-Chir. Trans.,' vol. lxxxvi, 1903, p. 395.

marrow much in the same way as we regarded the lymph-glands when we were dealing with diseases of the blood-forming organs. It was then shown that, as the cells of the lymph-glands are of very low organisation, in their case the differences which exist between organ-degenerations and cell-degenerations are at a minimum, so that they merge one into the other. We also saw that there is no means of judging whether certain forms of Hodgkin's disease are adenomata, or primary sarcomata of lymph-glands, and the same is true, though not to the same degree, of corresponding degenerations of bone-marrow. The marrow is also a lymphoid structure, and consequently the distinctions which ordinarily exist between degenerations of organs and degenerations of cells are in its case not strongly defined. At the same time, the bone-marrow is of higher organisation than the lymph-glands, so that this difficulty in distinguishing between the degeneration of marrow as a whole (osteomalacia) and that which localises itself in certain isolated cells (sarcomata) does not often occur.

V

CLINICAL ASPECTS OF SKELETAL SENILISM

Heredity can be proved in osteogenesis imperfecta and in osteitis deformans and is highly probable in osteomalacia. The causes of these degenerations are hardship, gonorrhea and syphilis. Sex is an important factor, osteomalacia being in the main a disease of women and osteitis deformans of men. Osteomalacia is precipitated by pregnancy. The beneficial effect of ovariectomy is probably the outcome of correlation.

Senilism of the marrow and of the shafts is an exaggeration of the changes characteristic of *normal old age*. The juvenile and adolescence forms are probably secondary to defects of development. Osteomalacia shows *endemic tendencies* and occurs in the *lower mammalia*. The course of skeletal senilism is progressive but intermittent, the prognosis unfavourable. Treatment is by arsenic and by removal of the ovaries (in osteomalacia).

• Heredity.

If we regard bending of bone as a fair criterion of defective calcification, and therefore as indicative of the presence of osteogenesis imperfecta, of osteomalacia, or of osteitis deformans, then we must include in our list such cases as that recorded by Dr. McOfficer, in the 'International Medical Journal of Australia.'* In this case a brother and sister were born with fractured bones. In the girl more than forty fractures occurred during the twelve years of the child's life, and in the boy over twenty could be remembered. In both cases there was much bowing of the femora and tibiae.

In Mr. Clinton Dent's case of osteomalacia† in a male, beginning at the age of four months, already referred to (p. 432) as an instance of osteogenesis imperfecta, there were indications of an hereditary tendency to the complaint. "The parents were healthy, but a sister had curvature of the spine; one cousin suffered from the same condition as the patient, another had scoliosis, and a third cleft palate." Here we have not only the statement of family heredity, but also evidences of association with an hereditary deformity, constituting indirect or transforming heredity.

* October, 1902, p. 486.

† *Loc. cit.*

In the report of a case of osteitis deformans by Dr. Stephen Mackenzie,* it is stated that "the patient was one of twins; his twin-brother was imbecile and died in early life in an asylum. Dr. Robinson (who attended him at the time of death) elicited the important information that an elder brother died a few years before the patient, at the age of fifty-two, crippled by a deformity of his lower limbs. The course of his illness resembled that of the present case, and he was believed by his family to have the same disease."

Another instance is given by Mr. Lunn.† The patient had a brother who was said to have died from cancer. Of another brother, aged 68 years, Mr. Lunn says: "He tells me that he has noticed his own head getting larger and his hat seems too tight for his head. I find both femora enlarged in their lower halves, and the right clavicle is decidedly larger than the left."

Mr. Bryant‡ states that one of the five cases originally published by Sir James Paget had been that of a patient of his own, and that he had had the opportunity of following it up for from ten to twelve years and that two brothers still living are beginning to show signs of the same disease. Of this family these were the only three members.

Dr. Pye-Smith,§ in writing on osteomalacia, refers to a case of extreme distortion of the limbs, thorax, and pelvis, recorded by Dr. W. J. Webb, of Chicago, in the 'New York Medical Journal' for March 21st, 1885, which occurred in a man, some of whose brothers and sisters had symptoms more or less like his own."

Yet another instance of heredity is given by Mr. Clutton. A woman with osteitis deformans of a single bone, beginning at twenty-five, and ending in amputation and death at thirty-five, had a brother who was said to have been in a hospital with non-venereal disease of the same nature affecting one humerus.||

Some of these examples are merely highly suggestive of hereditary transmission. By far the most convincing, and, indeed, the only instance of heredity which is entirely satisfactory, is one recorded by Dr. Walter Kilner.¶ In this case osteitis deformans occurred in brother and sister, and the clinical details and portraits

* 'Illustrated Med. News,' 1888, vol. i, p. 11; see also Dr. Robinson's article, 'Path. Soc. Trans., Lond.,' vol. xxxviii, 1887, p. 262.

† 'Clin. Soc. Trans., Lond.,' vol. xviii, p. 271.

‡ 'Lancet,' 1890, vol. i, p. 1182.

§ 'Principles and Practice of Medicine,' 4th edition, vol. i, p. 544.

|| 'Path. Soc. Trans., Lond.,' vol. xvii, 1891, p. 246.

¶ 'Lancet,' 1904, vol. i, p. 221.

leave no room for doubt about the nature of the malady. The interesting statement is made that, having regard to the premature senility of the brother, who was sixty years old, the disease began when they were apparently of the same age, though they had lived at a distance from each other for forty years. The sister had lived under comfortable circumstances in London and had previously enjoyed excellent health, but the brother had had frequent illnesses and had endured much hardship as an agricultural labourer. Neither of them showed any evidence of syphilis. The inference drawn from these facts by Dr. Kilner is that "neither climatic influence nor the mode of living has had any influence in the causation of the illness." They seem to indicate very clearly that the disorder in these particular cases occurred apart from circumstances, and was therefore a major variation.

Ætiology.

The *causes* of osteomalacia are said to be wet, cold, and over-work. "Osteomalacia is typically seen in certain districts in the half-starved servant woman with a large family, who works in the field exposed to wet and cold, suckling one child and heavy with another."* Hehre, writing in 1895, says that since 1881 he had seen forty-five cases in Heidelberg, and most of those affected were lean, cachectic, poverty-stricken, and prematurely old, though one third of the total were well-fed wives of butchers, bakers, and other flourishing tradesmen. Among other possible causes are gout (Sir J. Hutchinson) and syphilis.

Both osteitis deformans and osteomalacia have their physiological bases in certain changes of normal development, especially those associated with *sex* and *age*.

Influence of sex.—Osteomalacia is, as a rule, a disease of women and osteitis deformans of men. This is best explained on the ground that they are vices of development and, therefore, more liable to select those parts in which normal development is most vigorous. Women are of the more passive or "lymphatic" temperament, the tendency of their tissues being rather towards the formation of fat and lymphoid tissue than of muscle and bone. The lymphoid tissue of the bone-marrow is also more subject to disturbance in women, for the healthy rise and fall of growth and nutrition which takes place periodically, or at uncertain intervals (pregnancy),† renders

* Dr. Campbell Thomson, 'Encyclopedia Medica,' vol. ix, p. 5.

† A definite increase of red marrow with corresponding absorption of bone has been noticed in pregnancy.

their medulla more liable to that loss of equilibrium which constitutes disease. On the other hand, there can be no doubt that the hard tissue of the female skeleton is relatively of inferior growth; her bones are shorter, weaker, and slighter than are those of men. Hence it is but to be expected that women should be more liable to disease of the marrow and men of the compact substance of their bones.

The connection between the sex organs and the skeleton has important bearings on the pathology of osteomalacia. At puberty the leap forward in development, which is commonly imputed solely to sex changes, is as much skeletal as sexual, and the menopause corresponds in point of time with the physiological degeneration of the marrow. Correlation between these organs is, indeed, so close that any unusual rise or fall in the activity of the one organ is usually reflected in the other. Thus premature sex development is prone to bring with it corresponding changes in the skeleton; absence of testes in a young male determines a condition of bone growth which approaches that of the female, and absence of ovaries in the female is associated with the skeletal development approximating to that of a child. But perhaps most significant of all are the changes which take place in the bones and marrow during the heightened reproductive activity of pregnancy. These are shown by increased vascularity, especially in the pelvis, giving rise to decalcification and absorption,* sometimes manifested by aching pains in the bones similar to one kind of growing-pains of children (see p. 32).

This intimate correlation between the bones and the sexual organs amply accounts for the relation of osteomalacia to the functions of the ovaries, without seeking for any other explanation. It explains why the disease is prone to show itself at puberty and during pregnancy, why the ossa innominata of parturient women and the tibiæ of men are the bones most likely to be affected first, and why there is, as a rule, a subsidence of the disease during the period immediately following child-birth. Similar, though less marked, fluctuations are often produced by menstruation,† which is, as we have seen (p. 33), analogous to a miniature child-birth.

All these facts tend to the conclusion that osteomalacia is most apt to appear during periods of physiological skeletal excitement. It is on these lines, moreover, that we must seek the explanation of

* Hanau, 'Festschrift der Medicin,' 1892, No. 7; W. G. Spencer, 'Lancet,' 1896, vol. i, p. 1473.

† Alluded to by Fehling, 'Centralblatt für Gynäkologie,' Bd. xiv, 1890, p. 73; also Docker, 'Amer. Journ. Med. Sci.,' 1895, vol. cix, p. 499.

the immense improvement which so often takes place after the removal of the ovaries in osteomalacia. There is no occasion whatever to look for some chemical solvent, some peculiarity in ovarian structure, or for bacteria as an explanation of what is capable of being accounted for on biological grounds.

Osteitis deformans is not obviously affected by these sexual changes, probably in part because of the greater physiological stability of bone as compared with bone-marrow, and partly because it ordinarily appears at an age when the sexual organs are practically extinct.

The disastrous effect of pregnancy seems to be the natural corollary of the fact that osteomalacia is a presenility. The earlier in life a senilism occurs the more emphatically is it a senilism and a state of disease. Now, the effect of pregnancy upon the normal tissues of the pregnant woman is one of rejuvenation (see p. 32). But let any of her organs be in a state of incipient degeneration, and the pregnancy, which acts as a restorative to the body as a whole, will thereby indirectly so exaggerate the discrepancy as to precipitate a breakdown. There is reason to believe that most, if not all, of the degenerations may creep on insidiously for months or even years before they make themselves manifest by symptoms. Hence pregnancy may not in reality originate such diseases as pernicious anæmia, Bright's disease, arthritis deformans, or osteomalacia, but only so accentuate the conditions favourable to their appearance as to bring them forth when they already exist in a latent condition.

Relations with Normal Old Age.

The changes which take place both in osteomalacia and in osteitis deformans are in many respects much like those met with in the marrow and bone of the aged. But the resemblance is one of kind rather than of degree. It is, in fact, so grossly exaggerated as to be a caricature rather than a resemblance, and is such as we may imagine would result were senile degeneration to become a violently active instead of remaining almost a passive process. In the usual course of events the red marrow undergoes fatty degeneration into yellow marrow, and so remains or becomes gradually absorbed. But in osteomalacia degeneration shows itself in the forms of exaggerated proliferation and decay. The new material, so lavishly produced, is the outcome of descending development, and is therefore incapable of transformation into proper red marrow. It

can only undergo molecular degeneration. The process is suggestive of a senile degeneration taking place in one organ, while the rest of the body is still vigorous.

Rindfleisch,* in reference to this subject, says: "It has been noticed that the periosteum grows thicker in old people; that it becomes more vascular, and that those vessels in particular which pass from the periosteum to the surface of the bone become congested. These changes are associated with a peripheric (so-called 'concentric') liquefaction and absorption of the cortical layer of the bone. The sum total of these changes would make a valuable pendant to that absorption of bone from within which occurs in mollities ossium; and this comparison is all the more allowable as we really are acquainted with a senile mollities, differing in no essential point from the usual form of disease. May we adopt this view, and regard the mollities ossium of young people as a premature decay of the skeleton?"

At least three varieties of osteomalacia are recognised, namely, the juvenile, the adolescent, and the senile, and these run into one another by means of intermediate cases. We have an instance of senile osteomalacia under observation now.

It occurs in a lady, aged 80 years, who is in other respects sound. The disease first showed itself in extensive yielding of the whole spine. This was so rapid that within three weeks of its onset she became bent like a hoop, though she again returned to an almost straight condition after she had remained a few days in bed with weight extension. There was tenderness of some of the bones with intermittent aching. The bones affected were the pelvis, the femora (slightly), the vertebræ, and the lower ribs. There was some beaking of the pubic symphysis. Phosphates in the urine were increased to a very slight extent. The skeletal muscles rapidly became weak and wasted. Her niece, who looks after her, has more than once remarked on the capricious way in which the pain and tenderness increase or abate.

We have seen a case in a lady, aged 73 years, with almost exactly the same symptoms. Mr. Eve, in writing on "Senile Changes in Bones and Senile Diseases of the Osseous System,"† says of this form of osteomalacia: "Demange, who published two complete cases, with necropsies, in the '*Revue de Médecine*,' 1881, asserts that the extremities are usually unaffected in mollities of old age." He also says: "The lesions are localised, especially in the vertebræ; the spine becomes bent and the pelvis beaked."

* '*Pathological Histology*,' vol. ii, N.S.S., Transl., p. 275.

† '*Brit. Med. Journ.*,' 1891, vol. ii, p. 1194.

Geographical Distribution.

Osteomalacia is a sporadic disease, but is believed to show a tendency to occur endemically in certain parts of Bavaria, Württemberg, Baden, Alsace, and Switzerland. It is said to be met with more frequently along the Rhine than in other parts of Germany, and is common in some districts in India.

Zoological Distribution.

Osteomalacia occurs in sheep, pigs, deer, and in some other vertebrates.

Course.

Osteitis deformans and osteomalacia are characterised by irregularities in their course. Both disorders may for a long time be confined to a few bones before proceeding to affect the skeleton in general, or a sudden and seemingly capricious delay or arrest may take place in their ordinary course, but, to all appearances, only to gain a fresh impetus for further encroachment. These periods of quiescence may not be very conspicuous, and are often attributed to the action of some drug. They are sometimes alluded to incidentally as of very little importance, and in many cases, when brief reports are given, are doubtless not thought worthy of mention. But sometimes they are of most pronounced degree, as in a case of Dr. Howship's, reported in 1822, in which it was noted that "there was most marked inequality in the gravity of the symptoms. . . . Sometimes she became greatly better." In a still more remarkable case which we remember to have read, but the reference to which we cannot find, these periods of betterment again and again gave rise to the liveliest anticipations of recovery, and seem to have constituted one of the chief features of the disorder.*

Dr. J. W. Gross† has made some attempts to estimate the frequency of these recurrent or intermittent cases, though any such estimate of a feature which must often be omitted from the reports is necessarily very inadequate. He says: 'The growth is progressive and continuous, but in about 6 per cent. of all cases it is temporarily arrested, often not uniformly so.'

* See also Dr. E. Docker's case, 'Amer. Journ. Med. Sci.,' 1895, vol. cix, p. 499.

† 'Amer. Journ. Med. Sci.,' vol. clv, 1879, p. 40.

Prognosis.

In his article on "idiopathic osteopsathyrosis in infancy and childhood,"* Dr. Crozier Griffiths, who collected records of fifty-seven cases, says: "The prognosis of osteopsathyrosis is, as a rule, unfavourable, for when this tendency to fracture is once established it is apt to persist in spite of treatment."

The prognosis of osteomalacia is decidedly gloomy, though the patient "may recover spontaneously, even after many years." An instance of recovery is recorded by Prof. Berger† in a man, aged 20 years, whose disease began at the age of sixteen, and is all the more remarkable as it is said to be the first recorded case of spontaneous arrest and improvement in a male.

The prospects of senile osteomalacia are far more favourable. It is probably usually arrested within the course of a few years of its onset. We ourselves have seen at least two such arrested cases.

There seems to be no instance on record in which osteitis deformans, once fairly established, has disappeared, but as it is a disease of old age, death so often intervenes within a few years of its onset that the question of arrest and recovery is one of little more than mere speculation.

On the other hand, osteitis deformans starting in a single bone (usually the tibia) seems to remain confined to that bone, never becoming generalised.

Treatment.

Dr. Thorowgood‡ treated two cases of osteitis deformans with *arsenic* with great benefit. Mr. Butlin§ also says of arsenic that it is "the only drug which has appeared to produce a decided effect on the disease." He believes that one case was quite cured by it.

The most satisfactory form of treatment of osteomalacia is by *removal of the ovaries*. This seems to be nearly always successful when carried out before the onset of the menopause. It is strange that the natural menopause itself has not the same effect. The catastrophe of a sudden and violent cessation by artificial means is certainly far more effectual. We cannot find, though it has been suggested, that castration has ever been adopted for those rare instances in which osteomalacia has occurred in the male.

* 'Amer. Journ. Med. Sci.,' vol. cxiii, 1897, p. 426.

† 'La Presse Médicale,' 1905, vol. xiii, p. 249.

‡ 'Medical Times,' 1885, vol. i, p. 652.

§ 'Illustrated Med. News,' vol. ii, 1889, p. 291.

VI

PREMATURE DEGENERATION OR SENILISM OF JOINT AREAS: ARTHRITIS DEFORMANS

There are many *varieties*. These are determined by considerations of function, structure and age. The *course* is progressive, but intermittent. Arthritis deformans is sometimes induced by pregnancy. Structurally there is renewed proliferative activity, but the proliferation is aimless and abortive. The younger the patient the worse the disease. Hereditary cases have been recorded. Arsenic is the only drug of any use.

It is well known that the aged are subject to osteocopic joint-pain, and that their articular cartilages are prone to wear down, while the bones which help to comprise the joints tend to throw off osteophytic growths. Changes of this kind by exaggeration become mild forms of arthritis deformans, and it is not possible to say where normal senility ends and osteo-arthritis begins. The two run into one another.

One of the most characteristic features of arthritis deformans is the variety of its manifestations. Each pathological change, in short, has its corresponding physiological precedent, both in respect to function and to structure.

Thus in the first place changes are most prone to begin in those joints which are most used, so that in women a different set of joints is generally implicated than is the case with men. This fact was pointed out by Senator, and has been particularly referred to among others by Mr. Arbuthnot Lane, who has made use of the British charwoman to exemplify his remarks.

In the second place the malady may affect many joints or one only. One of the joints which undergo most wear and tear and are consequently most liable to be crippled in old age is the hip-joint. It is also one of the most frequent seats of arthritis deformans, giving rise to the well-known "*morbis coxæ senilis*."

In the third place the structures which comprise the joint area may all be affected together, or one may be disordered to a far greater extent than others. Each tissue has its own standard of development, and joint senilism has been divided into three main

groups according as (1) the synovial membranes, (2) the cartilage, or (3) the bone is the starting-point and chief seat of the disease. Prof. Osler, in addition to the mono-articular form, to the general progressive form, and to that with Heberden's nodes, refers to the vertebral variety (spondylitis deformans).*

Further varieties result through variations in the *course* of the complaint, so that we have acute and chronic cases, the former in extreme instances pursuing their career with the rapidity of a fever, or even simulating fracture; and the latter at the other extreme, going on for many years but causing very little trouble, to end in ordinary senile "rhenmatics." In its acute form, or during an exacerbation of the more chronic form, the disease has often been mistaken for acute microbial rheumatism.

Age also provides three varieties, the (1) mono-articular form of old age being very different from the (2) more widespread and crippling form commonly met with in middle age, and this again is so distinct from the (3) acute disease of early adult life that the latter is believed by some competent authorities† to be a totally different disease. In fact, a similar scepticism is felt as to the identity of the acute and chronic forms to that which exists in regard to the relation of acute leukaemia to chronic leukaemia, acute Bright's disease to chronic Bright's disease, and acute yellow atrophy of the liver to ordinary cirrhosis.

Heredity.—According to Prof. Howard Marsh‡ the juvenile form is sometimes hereditary, and he says that E. C. Seguin has met with three cases in the same family, in children between the ages of two and a half and four years.

Course and Prognosis.—Generally speaking the earlier the disease occurs the more rapid is its course. This course is always progressive, but is broken by periods of comparative quiescence, which are, as a rule, spontaneous, and are so marked that in some cases the malady seems temporarily to disappear. Of the general progressive form Prof. Osler says: "In many cases, after involving two or three joints the disease becomes arrested, and no further development occurs," and respecting the acute variety, Dr. Howard remarks (quoted by Osler), "in several cases of this form marked intervals of improvement have occurred, the local disease has ceased to progress, and tolerable comfort has been experienced,

* 'The Principles and Practice of Medicine,' 6th edit., p. 390.

† See Dr. Hale White, "On the Pathology of Acute Rheumatoid Arthritis," 'Guy's Hospital Reports,' vol. lvii, 1902, p. 9.

‡ 'Diseases of the Joints,' 1st ed., p. 68.

perhaps until pregnancy, delivery or lactation again determines a fresh outbreak of the disease." But as a rule "the complaint, although chronic, progresses intermittently by acute stages"* until the joint becomes useless.

Many writers dwell on the importance of *menstruation*, *pregnancy*, and *lactation* in accelerating or initiating the malady.

Structure and pathology.—"The osteo-arthritis met with in old persons begins, there can be no doubt, as a purely degenerative change in the cartilage and synovial membrane, soon extending itself to the bones, and although there is added a form of inflammatory action provoked by injury inflicted on the imperfectly nourished joint structure . . . degeneration is throughout the disease the main process."†

The dominant change in the joint cartilage of ordinary cases is one of renewed activity. "Histologically the change consists in a proliferation of the cartilage capsules, so that each becomes replaced by from eight to twenty large elements; the matrix at the same time splits into fibres in a direction perpendicularly to the articular surface" (Drs. Fagge and Pye-Smith). The cells arrange themselves into columns as if about to begin the formation of fresh cartilage or of bone. But this activity, though it may be quite as spontaneous as that which initiates development, is no longer orderly and formative, but is irregular and decadent. The activity of the cell is exhausted in the work of multiplication, and the pressure of the cell masses on adjacent cartilage results in the reduction of the cartilage to a lower order of tissue and in its subsequent absorption. In the course of this regression the cartilage is taken part of the way towards bone formation, fibrillation and calcification taking place, but not ossification. Similar inco-ordinate activity sets in in adjacent bone and fibrous tissue, resulting in the deterioration and absorption of sound, well-organised material on the one hand, and the deposition of irregular and uncalled-for deposits of material (small osteomata and enchondromata) on the other. The aim is evidently not to build up but to break down, but the whole process is needlessly energetic, so that the natural decay of old age is exaggerated and distorted. The change approaches to that of a cancer process, but is more restrained; indeed, in severe cases, when the sprouting tissues fill out the joint areas until they form huge nodes destitute of function, the process is as truly malignant

* Dr. Murrell, 'Practitioner,' vol. lxxxv, 1910, p. 643.

† 'Diseases of the Joints,' Prof. Howard Marsh, p. 53.

from the local standpoint as any leukæmia or locally malignant cancer.

Concomitants of degeneration.—An organ which has undergone degeneration has been thereby rendered more susceptible to the attacks of micro-organisms. This is, in all probability, the explanation of those bouts of inflammation which are so liable to supervene in joints affected with arthritis deformans. In fact, in many cases of this disease we have to do with a mixed condition, the degeneration being modified by the attacks of inflammations which have passed over it.

Treatment.—Though, in most instances, arthritis deformans apparently arises without cause and continues intermittently, irrespective of treatment, yet there seems to be no doubt that hygienic measures are of some value in inducing or prolonging the intervals of amendment, and perhaps in mitigating the severity of the whole morbid process. Professor Osler says that “fresh air and careful attention to personal hygiene are most essential. The question of diet is of the first importance. There is one rule—let the patient eat all the good food he can digest.” The value of social influences, and of invigorating air, as accessories to the frictions, hot donches, and other paraphernalia of the spa, as well as of protection from cold and gentle exercise, is recognised by Professor Howard Marsh and other writers. Apparently the only drug of any real value is *arsenic*. Both Professor Osler and Dr. Fagge refer to this drug with approval, and the opinion of the latter is emphatically endorsed by Dr. Pye-Smith.

The Developmental Diseases of the Skeleton considered as Variations.

We have already shown reasons for regarding achondroplasia as a major, and rickets as a minor variation of *growth*. There are equally good reasons why we should look upon the infantilisms and senilisms as regressive variations of *development*.

Any of them which occurs in marked form and without ascertainable cause may be suspected of being a major variation, but if it be hereditary it is without doubt of that nature.

On the other hand, if it be definitely the result of a cause it is a minor variation. It is then not heritable, and is usually more amenable to treatment.

Most, if not all, infantilisms as well as those senilisms which

declare themselves in early life are major variations. But the arthritis deformans of old age is in all probability invariably a minor variation, seeing that it is no more than a slight anticipation of a normal event.

Summary and Conclusions to Part III.

Examples have now been given of the way in which individual organs enter into a state of disease by falling short of, or exceeding, their normal growth, or by becoming stayed or unduly accelerated in their development. We have seen that the diseases of this description, though biological in origin and in constitution, become pathological in the event. Organs so affected, being no longer in unison with the rest of the body, so hamper or otherwise derange its action that they become to all intents foreign bodies or parasites within the somatic cavity.

As variations or diversions from the ordinary beaten track of growth and development, these disorders fall into one or other of two great divisions. They are either the result of causes (of a depressing, insanitary, or toxic character) acting in conjunction with a concealed factor (minor or continuous variation), or they are solely the outcome of this cryptic influence, and are major or discontinuous variations. In the former case they come within the definition of acquired characters, and are therefore not hereditary, whereas in the latter they are not only striking in character, and incurable or lethal, but show evidences of heredity. Though many examples of these diseases have been given, and the modifications which they undergo under the influence of locality, age, structure, function, and other circumstances have been pointed out, to some of the most important organs, such as the heart, the lungs, the thyroid, the pituitary, no more than a passing reference has been made.

Though it is not within the scope of this book to embark upon such an extensive subject as the diseases of post-natal growth and development of every organ in the body, one other organ must be referred to, if only because of the splendid illustration it affords of the kinds of disorders with which we are dealing. This is the *thyroid gland*. The thyroid is an organ which can so readily be observed and has such precise functions that its derangement is clearly to be detected. It, moreover, helps to bridge the gap which exists between those disorders which affect isolated organs and those which are of the whole man.

The thyroid gland is sometimes *dwarfed* without being obviously defective in quality, and this is the least of the anomalies to which it is subject.

At other times it is *gigantic* in size and is correspondingly excessive in function. This is the parenchymatous enlargement of Graves's disease. It is evidently the outcome of a spurt of advancing development, for it occurs at a time of life when the gland is usually approaching its zenith, and in a sex which is peculiarly prone to physiological fluctuations of thyroid activity.

But there is another parenchymatous goitre, and this is evidently the result of a loosening of the restraints of growth which is characteristic of declining development. In this case quality deteriorates, so that the function of the gland is but slightly, if at all, increased, and it is liable to outgrowths of adenomata due to similar redundancies of constituent thyroid cells.

Of these two forms of overgrowth that which constitutes the dominant feature of Graves's disease is a progressive variation, whereas that which is the expression of declining development is a regressive variation.

Defective development or *infantilism* of the thyroid accounts for many cases of cretinism, for the gland of defective development is not only inadequate in itself, but is peculiarly apt to undergo premature degeneration.

Of degeneration or *senilism* there are two forms, though these are connected by intermediate links.

The thyroid is liable to undergo enormous increase of size, forming great fleshy pendulous masses, which hang upon the neck like well-filled pouches. But these overgrowths are not of the active constituents of the gland, but of deteriorated single cells (adenomata) and of fibrous tissue. This fibrous tissue contracts upon and strangles the gland, so that the mucous secretion, unable to escape, is pent up and accumulates in the form of cysts. Hence, though

there may be considerable overgrowth, activity is not heightened, but impaired, constituting degenerative hyperplasia. In extreme cases the function of the thyroid is so effectually destroyed that cretinism or myxœdema results. This form of degeneration is apt to supervene upon the parenchymatous enlargement.

At about the time of the menopause symptoms of myxœdema occasionally appear as the result of premature senile waste (senilism) of the gland without previous overgrowth. This is the hypoplastic form of degeneration, and is that which has closest affinity with normal senile decline. Both this and degenerative hyperplasia are regressive variations, for they indicate a reversion to a period of evolution when life terminated earlier than it does now.

When the thyroid gland is stricken with incapacitating disease so that its function is destroyed the whole body is involved in the catastrophe, so that its growth and development are thrown into a state of disorder. The generalised infantilism or senilism so produced will presently be discussed, together with similar disorders which result from the action of other causes.

PART IV

THE DISORDERS OF GENERAL GROWTH AND DEVELOPMENT

SECTION I

The Biological Basis

I

INTRODUCTION

The excesses and defects of growth, accelerations and inhibitions of development which constitute disorder are of that nature because they are a decisive departure from custom. Abnormal defect of growth is **dwarfism**, excess, **gigantism**; abnormal immaturity is **infantilism**, and premature senility, **senilism**; prematurity of progressive development is **precocity**, and delayed regressive development is **centenarianism**. There are also four general disorders or anomalies of sex, to wit—**under = development**, **over = development**, **feminism**, **masculinism**.

WE have hitherto been concerned chiefly with the disorders of growth and development of cells and of organs. Now we have to consider disorders of the same kind affecting that combination of cells and organs which constitutes the man. But before entering upon this subject it is important to realise that we can no more confine our attention to the single man than we can to the single cell or the single organ. It is just as impossible for the man as it is for the cell or the organ to thrive alone. In combination with others he lives a corporate existence, and must be considered as the unit of a larger body—the body politic. His value, indeed, is entirely relative, so that when we say a man is tall or short, long lived or short lived, immature or prematurely old, the terms are used in a relative sense, according as he is above or below the line of general growth and development.

The standards of height and weight and of length of life differ in different countries. Thus among the Bosjesmans the normal limit of old age seems to be attained before the fiftieth year of life, but in our own country a man who dies at fifty has not reached beyond middle age. So also among the Japanese a man of 166 cm. in height is tall, but the same man in Europe is undersized. The

reasons for this diversity will appear later on. It must be obvious that our own standard must be determined by the averages of a large number of men and women of the most highly civilised nations.

Definitions and Divisions.

Errors of growth.—Before the errors of general development can be dealt with, it is necessary to separate from them the errors of growth. The latter have to do with size or quantity only, and not with quality. A defect of growth is *dwarfism*. In a well-formed dwarf nothing is altered except his size, for he may be in every other respect a normally developed man. The excessively grown man, who reaches a stature of, say, 2 m., is a *giant*. He lives a normal life, has children, and shows no conspicuous sign of morbidity. But this is not quite correct, for, as a matter of fact, the man of excessive growth resembles the organ of excessive growth in that his overgrowth brings with it some of the phenomena of failure of development. But the point to observe is that he is overgrown in the first place, and the marks of degeneration are secondary to it. They are incidental, not essential. In overgrowth of slight degree there is usually no perceptible lack of vitality or other sign of want of tissue control, but the greater the overgrowth the more likely is there to be some weakness, some irregularity of growth, or some manifestation of premature old age (*acromegaly*). The common impression that men of excessive growth are more sickly, have less stamina, less mental capacity than men of average size is probably correct, though the exceptions may be numerous.

Errors of development.—It has been observed that errors of development may be of two kinds. The development may be delayed to an abnormal degree, so that infantilism results, or, on the other hand, it may be premature and constitute senilism. But such a division is not adequate, for the delay of development may take place either during its earlier stages or in its decline. It is to the first of these that we should apply the term *infantilism*, but to the second, or abnormal delay of the downward course of development, we may give the name of *centenarianism*, though, indeed, most, if not all, of those who live over the age of eighty-five may be suspected of coming under this head.

So also, in the case of premature development, there is a difference between that prematurity which begins during the earlier years of life and that which takes place in the later years. Prematurity affecting the progressive ages generally goes by the name of *pre-*

cocity, and that of the regressive ages is termed *presenility* or *senilism*, according to its degree.

But we have not yet reached the limits of division, for the body as a whole differs from its collective organs in that the body possesses sex, while the organs have no such distinction—save in the case of the sexual organs, and their satellites alone. Hence we have two further divisions, one of which is termed *feminism* and the other *masculinism*. In feminism the male organs are not only in abeyance, but the whole body shows more of a feminine type of development than is natural. In masculinism, on the other hand, male characters are manifested in women. Hence in both cases general development is thwarted or thrown out of its natural groove. These different divisions may be tabulated as follows:

1. Growth.

- (1) Defective=dwarfism.
- (2) Excessive=gigantism.

2. Development.

- (1) Delayed or arrested.
 - (a) During progressive periods=infantilism.
 - (b) During regressive periods=centenarianism.
- (2) Premature.
 - (a) During progressive periods=precocity.
 - (b) During regressive periods=senilism.

3. Sex.

- (1) *Sexual* precocity.
- (2) *Sexual* protraction.
- (3) Feminism.
- (4) Masculinism.

It should be noticed that some of these conditions can hardly be termed “disorders,” however elastic our use of that word may be. At the same time they undoubtedly represent states of faulty growth or faulty development, and as such are included here for the sake of comparison and of completeness.

Attention must also be directed to our use of the words “feminism” and “masculinism,” seeing that one of these words is now more commonly used in an exactly opposite meaning to that which it bears here. But a little consideration must convince anyone that the popular use of the word, as applied, for example, to the so-called feminist movement, is wrong, and that where a distinctive designation is desirable the proper term to use would be “masculinism.”

II

ADAPTATION; CORRELATION; ASSOCIATION

Adaptation is rapid when the characters to be changed are of the minor or more flexible sort. Bodily proportion is the result of prolonged adaptation. **Correlation** is adaptation rendered automatic by custom. In disease *adaptation of growth* is well shown in rickets and achondroplasia. It is most perfect in those parts most intimately related to the organ affected. *Adaptation of development* is seen when chronic Bright's disease is *associated* with cirrhosis of the liver, or when defective development of the sex organs is associated with opposite sex characters. Infantilism results when there is adaptation of the whole body to local defects of organs, or to external or internal devitalising circumstances. Occasionally infantilism occurs as a special disorder independent of circumstances.

A. Adaptation.

It is recognised that every living creature is plastic to its environment. There is, in fact, no limit to the capacity of organic beings to accommodate themselves to their surroundings. This is strikingly manifested in the alterations which unicellular organisms can be made to assume by a persistent education extending over many generations. A similar adaptability is shown by the Metazoa, and in their case the facility with which the accommodation takes place is sometimes so conspicuous as to suggest that each protozoon constituent of the complex animal is separately engaged in making the requisite changes. In other words there is, as we have seen, reason to believe that, even in animals of the highest complexity, the capacity for adaptation is to be reckoned on a unicellular basis, as well as on that of the individual as a whole. Hence the changes which take place in—say—a man under the influence of environment are the sum total of those which have gone on in what is tantamount to many generations of his cells. Indeed, if the cell be the ontogenetic equivalent of the protozoon, and the organ the like equivalent of the primitive organism, it necessarily follows that there is one adaptation of cells, another of organs, and yet another of the complex animal, each primary constituent of the body working out its own development at a rate which inversely corresponds with its status in the evolutionary scale.

But what we are now concerned with is the capacity of the highest Metazoa, in particular, to respond to those influences which affect their growth and development.

We must first premise that the mean *size* of any animal is in accordance with the circumstances in which it is placed. The prehistoric hippopotamus whose bones have been found in the island of Crete was a small animal, no bigger than a good-sized dog, whereas the hippopotamus of the present day is one of the biggest of quadrupeds. The difference in size is said to be due to that fact that the smaller animal lived among the rivers of a comparatively open country, whereas the modern hippopotamus must be of heavy weight in order to crash through the close underwood of its accustomed forests.

After the same fashion the Slav or Tentou, who admires bigness, has been accustomed for centuries to the use of coarse tools, to heavy waggons and clumsy cart-horses, and whose ambition still lies in the direction of big houses, big guns, big ships, and big men, is himself a man of big size. On the other hand, the Chinese, who aims at neatness and skill rather than bulk, who lives in little, fragile houses, and is accustomed to light furniture and small, natty tools, is a little man.

As it is with the man as a whole and his possessions, so also is it with his different parts. The relation of these parts in regard to size varies with circumstances. It varies with age, for what is proper to one time of life is disproportionate to another. There is a different standard of proportions for the baby, the adult, and the aged. The baby compared with the adult has relatively short limbs and a big head. Some of the proportions, especially in regard to the lengths of the body and of the lower limbs, remind us of the standards set by the higher apes. In old age these measurements are altered by the yielding of the spine, and by the shrinking of other parts, so that eventually the shortened, stooping figure, the projecting head, corrugated features, overhanging eye-brows, increase in general growth of hair, shuffling walk, and use of a stick, are again reminiscent of a simian ancestry.

Just as the hippopotamus owes its vast bulk to the rank growths of woody vegetation bordering the rivers in which it lives, so the dwarf of Central Africa partly owes his size to the nature of the interfluvial forests which constitute his home, his very smallness enabling him to insinuate himself under, over, or between the tree-trunks and creepers which obstruct his passage.

Another important factor in fixing, or even producing, the littleness of the forest or desert dwarf is the smallness of his bow and

arrows. It is noteworthy that such widely distributed peoples as the dwarf Aetas of the Philippines, the Bosjesmans of South Africa, and the equatorial dwarfs of Central Africa all use small bows and tiny poisoned arrows. Though an important exception occurs in the Andaman Islanders, who use a big, heavy weapon, yet, on the whole, the small bow and the poisoned arrow must be looked upon as highly important items of the dwarf's surroundings and influential factors in his development. The poisoned arrow is to the forest dwarf what the poison fang is to the snake. Snakes which crush their victims by sheer muscle force are generally big, thick reptiles; those which sting are usually small and comparatively feeble. Where weapons and tools are scanty the nature of the favourite weapon must have great influence upon the character of the people who use it.

Whatever is true in this respect of a weapon or tool holds good with still greater force of a part of the individual, such as an arm or a leg, for these also are the weapons and tools with which the man hunts, fights, and works. Indeed, the word "arm," as applied to the segments of a limb, is derived from the same root as the "arm," which means a weapon. And so we come back to the fact that there is constant action and interaction going on between man and material, between one part of him and another part, and conclude that bodily proportion is the sum total of this adaptation to circumstances.

As George Herbert says :

"Man is all symmetrie,
Full of proportions, one link to another,
And all to all the world besides :
Each part may call the farthest, brother :
For head with foot hath private amitie,
And both with moons and tides." *

Hence the relation which any part assumes with other parts becomes at last permanent and automatic. In other words, one part of the body is *correlated* to another part, or to the body at large. The relations between correlated parts is indeed itself virtually that of an environment. Thus if a walking-stick act as an environment to the upper limb and influence its growth the hand itself has still more influence of a similar character. So accustomed are associated parts to act together that the decline or fall of one often brings about similar results in its fellow. Indeed,

* 'The Church,' lxvi, "Man."

it is possible to formulate a generalisation to the effect that *parts which are accustomed to act together under normal conditions are also prone to be associated in disease.*

From this it will be understood that, strictly speaking, *correlation* is not only the reciprocal relation of one part to another part, but of the part to the whole, whereas *adaptation* is the response of the part, or whole, to its general environment. Correlation is the result of innumerable adaptations or adjustments, the habit of co-operating being so confirmed as to become automatic. It is adaptation stereotyped. Hence correlation or association is an important factor in the production of general infantilism, for if an organ be blighted in its development as the result of regressive variation, it is possible that the influence of correlation may lead to similar failure in the development of some other organ or of the whole animal.

Adaptation and Correlation in Disease.

A. Adaptation and Correlation of Growth.

Adaptability is evidenced in disease as well as in health, though it is shown in different degrees under different circumstances. The slower the progress of a growth malady and the earlier the age of its occurrence, the more perfect is the adaptation.

In its least perfect form it is manifested in the adult limb from which some inches of bone have been removed. In such a limb the muscles and other soft parts shorten so as to adjust themselves to some extent to the altered conditions, but some bulging and wrinkling will continue for the rest of life, gradually diminishing, it is true, but always bearing testimony to the sudden removal of an important segment of the framework of the body after growth and development had ceased.

Adaptability is far better shown when bone is removed during childhood, or when its growth is stopped by destruction of the growth-centre at one of the epiphyses. It is shown again in such a disease as rickets, where the relation of the growth of the soft parts to the growth of the long bones of the limbs is so good that at first sight there seems no disproportion whatever between them. Yet, although there may be no such bulging of muscles as would amount to deformity, some rickety dwarfs undoubtedly have a disproportionate growth of muscle and an unusual degree of muscular strength. This inordinate strength may be in part due to the fact that their muscles form shorter levers, and therefore act at a

mechanical advantage as compared with the muscles of men of average height. It may also, according to the late Sir G. M. Humphry, be partly the result of the bending, which is a mechanical help to those muscles situated on the concavities of the bowed extremities. There is still better adaptation in the subjects of achondroplasia, for the reason that this disorder begins at an earlier time of life. Being a foetal disease the adjustment of the soft parts to the requirements of the skeleton is so far complete that at first sight it seems to be all that can be desired. But even in this case the co-ordination is not perfect, for it often happens that the bones remain too thick and the muscles too big, adding to the ungainliness produced by the disease without conferring adequate compensating advantages.

If this adaptability be sometimes imperfect in parts which are in direct physiological relation with the faulty organ or tissue, it is still more imperfect in those which are not so directly connected with the defective part. Hence, while it is true that the rickety man or the achondroplastic has limb muscles which are usually a little too big for his needs, the same man is possessed of a trunk and head still more obviously out of keeping with the length of his upper and lower extremities. Yet, even in this case, adaptation takes place, though to a less degree. The trunk of one of these dwarfs may, in some instances, be about the length of that of the average human being, though it is usually shorter. But here, again, the degree of adaptation is variable. Some of these unfortunate people go their way through life with short, crooked limbs, very long bodies, extended necks, and big, misshapen heads, looking as grotesque as mediæval gargoyles; others seem to be dwarfed in every direction, and consequently have much less the appearance of deformity. Those who have short bodies are obviously much better off than are those with bodies of ordinary length.

So far we have been dealing with affairs of growth rather than of development, but it is clear that we can deduce certain generalisations which apply to both. We notice firstly that there is in health a correlation of growth, so that all parts of the body conform to a certain standard, though this standard is by no means precise or fixed on one uniform model. Natural correlation of growth also continues under abnormal conditions, so that the normal parts of the body are made to conform to the abnormal. But this faculty of adaptability is variable. Sometimes it is so perfect that there is hardly any deformity, whereas at others adaptation is almost absent, though the circumstances may seem alike. Other things

being equal, it is most complete in those parts having the closest physiological relation with the deformed organ.

B. Adaptation and Correlation of Development.

If the development of one part of the body be delayed or arrested there is always a tendency for the development of other parts to come down to the same level. And here it is important to notice that the adaptation which is consecutive to a stoppage of growth of some important organ of the body is not always one of growth alone. It may take the form of an alteration of development.

Thus it has been remarked that caries of the spine, taking place in infancy, may lead to very decided developmental delay. In such cases it is of course highly probable that the poor health and physique which was responsible for the tubercular disease also accounted in part for the delay of development.

We have just seen that the correlation which is to be observed in health is the basis of that which we term "association" in disease. Correlation, adaptation and association are, indeed, all the outcome of the same process. Thus when we say that "idiopathic" Bright's disease of the kidney is "associated" with cirrhosis of the liver, or that pernicious anæmia is "associated" with degeneration of the spinal cord, we mean that there is some correlation between the organs involved, and that the disorders occur together as the result of an attempt on the part of the organism to equalise matters by adapting the circumstances of one organ to the morbid condition present in another. This adaptation is, of course, best seen under physiological or quasi-physiological conditions. Thus, for instance, in the infant of somewhat defective brain power there is a tendency for the whole body to be of small size. This is evidently an arrangement to make the best of circumstances, for with an adequate supply of brain material it is to the advantage of the individual that the functions of the brain should not be diverted from the more important office of mind to the less important uses of muscle and bone.

Another possible example of the way in which correlation of growth and development continues under abnormal conditions is furnished by the sex organs, and their relations with general bodily development. In the course of long ages of evolution it has become established as a custom that at a certain time of individual development the sex organs should emerge from their previously dormant condition, should ripen, and become capable of performing their

proper task of pollination, or ovulation and fructification. This important event coincides with the perfection of bodily development, with the completion of the building of the skeleton and fusion of its epiphyses. It corresponds with the accomplishment of the development, of the bones, ligaments, and muscles. Other soft parts usually associated with these structures undergo rapid increase at the same time. But of all the changes which take place at puberty, those of the sex organs are most conspicuous, have attracted most attention, and are naturally looked upon as the dominating factor in the situation. It is generally believed that the spurt which takes place in the growth and development of other organs at puberty is the direct result of a stimulus emanating from the sex organs, this stimulus being accomplished by means of a secretion from the ovarian follicles in the female, and from the testes in the male.

It is apparently corroborative of this view that when there is some conspicuous (discontinuous) variation in the construction of the testes or ovaries, other parts of the body usually undergo sympathetic changes. This is best observed when the sex organs mature several years earlier than is their custom, for under such circumstances the skeleton and the soft parts, as a rule, also undergo premature development. In these cases sexual precocity may evidently come first, and be followed by the precocious development of other organs.

Yet it is very doubtful if this precocity is caused by any special secretion. No artificial supply of sexual fluid, no matter in what way it is given, is of any value in stimulating growth or development. Experiments which have been made again and again to this end, under all sorts of conditions, have invariably been unsuccessful. Moreover, castration of males or females just prior to puberty does not, as a rule, greatly interfere with bodily development. Indeed, some men who have undergone this mutilation in infancy are of very good development, except in regard to their primary and secondary sexual characters. It is true that if the operation be done at a very early age the male so treated assumes more or less of the feminine type, while the female becomes to some extent masculine. The mutilation, in short, results, not so much in a change in the quantity of general development, but in its quality, and this quality is altered only in respect to sex, and in no other way. So also similar results ensue at the natural menopause, when the reproductive organs become virtually extinct. Occasionally this change does not stop at mere passive sexlessness, leaving the man or woman a neuter, but virtually transforms the sex, so that the woman becomes manly, the man womanly.

All this is quite different from what we should expect were the special sex organs the direct *cause* of that rapid development of bone and muscle which takes place at puberty. If this were the explanation the effect of the destruction of these organs ought to be an invariable stunting of growth. There should be infantilism and never hermaphroditism.

It seems much more likely that we have here another instance of normal correlation continued under abnormal conditions. It is the custom for certain changes to keep company with one another at certain epochs of life, and out of this habit has grown a correlation which continues to manifest itself when circumstances are dislocated. Undoubtedly the sex organs are predominant in this relation, just as the brain is the dominating organ in the dwarfism or infantilism of microcephaly. In each case we see a similar process at work. Certain parts of the body accommodate themselves to the altered circumstances of some organ to which they ordinarily act as satellites. In health we give this mutual accommodation the name of "correlation," and recognise that the orbit made by the dependent organs is not a circle, but an ellipse, because of the disturbing factors outside the central organ which tend to attract in other directions. Under abnormal conditions the influence of these outside circumstances is much stronger. Hence, the orbit which is taken by the satellite organs is more erratic, even to the extent in some instances of leaving the customary track altogether. In other words, there are far more exceptions to the rule of correlative association in disease than in health.

Other Causes of Infantilism.

These are not the only instances of the imperfection of one organ apparently inducing a corresponding imperfection in the rest of the body. Undergrowth or under-development of the bones, of the brain, of the sex organs, are not the only conditions which lead to infantilism. *Degenerations*, such as fibrous degeneration of the liver, kidneys, pancreas, spleen, or muscles, may be a cause of infantilism. It is highly probable that the degeneration acts in a double capacity, partly as a direct cause, by reason of the debility it sets up, and partly by correlation. Sometimes defective nutrition seems to be by far the more important of the two. This is probably true of the infantilism produced by heart disease, either pre-natal, or occurring during infancy.

In some instances there is reason to believe that correlation is the

more important factor. This may very well be the case in some instances of infantilism associated with hypoplasia of the heart and arteries. A similar explanation may also possibly hold good in some cases of pancreatic infantilism, which are based upon defective development or premature fibrosis of the pancreas. This explanation is still more likely to be correct when the infantilism is associated with cirrhosis of the liver, or with chronic Bright's disease; or, still more, with splenomegaly or pseudo-hypertrophic palsy. In all these cases it is true that we have a condition which leads either directly or indirectly to imperfect nutrition, but if such imperfection would alone account for infantilism we should expect to see infantilism much oftener than we do. As a matter of fact it is well known that any debilitating cause is capable of delaying the course of development, though whether this delay can be so pronounced as to deserve the name of "infantilism" is another matter. In those dwellers in great cities who live below the poverty line in crowded and dirty tenement houses, it seems pretty certain that there is a far larger proportion of people with unequal or retarded development than there is among those who live under conditions of health and comfort. But it is equally true that one meets with positive infantilism among all classes, and that even among those who are most poverty-stricken it is by no means common. Hence, though we must look upon unfavourable hygienic conditions in general as causes of infantilism, they must be regarded more as a predisposing, or indirect, rather than as direct causes. So, for similar reasons, we cannot believe that the spinal curvature, splenomegaly, pseudo-hypertrophic paralysis, or other cause of infantilism produces this condition solely because of its debilitating effect on the human body. It is much more likely that the cause is of a mixed character, and that the mere debility plays a very subordinate part. Of much greater importance is that innate property possessed by the organs of the body of adapting themselves in their growth and development to the exigencies of whatever circumstances of a physiological or metaphysiological nature may be forced upon them.

It is often, in short, impossible accurately to say what is the cause or denomination of a particular example of infantilism. We can no more be sure of this point than we can determine the exact causes of certain cases of premature old age.

In fine, any substance or circumstance capable of delaying development is a potential cause of infantilism. Thus we often hear that a baby is, for a time, of stunted development owing to whooping-cough, measles, diarrhoea, insufficient food, or some similar cause.

After a time, by means of feeding, cleanliness, change of air or other hygienic attention, this temporary backwardness is overcome, and development proceeds apace. But let the cause of debility be unusually pronounced, and, what is still more important, let there be in the child a latent tendency to defect of development, and infantilism results.

To all intents the *toxins* may be regarded in the same light as insanitary air and other surroundings. They represent insanitation in a concentrated form. The organs and cells are for a period bathed and surrounded by fluids highly detrimental to their vitality, comparable with individuals in an extremely insanitary neighbourhood, or living for a time in homes reeking with poisonous effluvia from stale human emanations. *So far as their effect on growth and development is concerned, no fundamental distinction can be drawn between the poisons produced by the toxins, say, of diphtheria or measles, or influenza, or wine, or syphilis, on the one hand, and those produced by leakage from gas pipes, or sewers, or by re-breathed air on the other. Nor can we separate from them the psychical toxins, such as failure in business, destitution, disappointment in love, or social disaster of any kind.*

Among the most definite and important of these poisons are the toxins of wine and of syphilis, and of the infective fevers. Many cases of general infantilism are largely due to repeated attacks of infantile diarrhoea, to malaria, enteric fever, influenza, scarlet fever, or to tuberculosis.

But this does not exhaust the ætiology of infantilism, for one of the most conspicuous of all does not come under the denomination of either of these causes. This is *cretinism*. In reality cretinism is no more than the array of symptoms produced by infantilism or senilism of the thyroid gland. But so also is syphilitic infantilism but one of the symptoms produced by the toxin of syphilis. It is plain, therefore, that cretinism must be classified with general diseases of development, though it is secondary to a pre-existing developmental disorder of a particular organ.

Then *defective action of the pancreas* may apparently in some cases be the origin of infantilism, chiefly because of the defective nutrition to which it gives rise by impairment of the function of digestion.

Hence, to sum up the causes of infantilism, we may say that any unhealthy condition of air, house, food, water, or soil acting upon the human being during the early years of his post-natal existence must be regarded as a favouring or indirect cause. But the dominating cause is, as a rule, local, and consists in some primary

disturbance of the development of some particular organ. Under such circumstances whatever organ is responsible gives its name to the infantilism, so that we have amongst others, *cerebral, sexual, pancreatic, intestinal, hepatic, renal, osseous, cardiac, myopathic, thyroid infantilisms*.

One other form of infantilism still remains. All those hitherto mentioned are symptomatic, that is, they are mere manifestations of some other disease or disease agent, and are not essential diseases. They are no more primary diseases than is the dwarfism of achondroplasia the disease itself. Nothing shows this more clearly than the fact that, leaving cretinism on one side, the general infantilism is only an occasional or even rare accompaniment of the local morbid condition:

We shall have to refer to a form of infantilism which differs from the symptomatic forms, in that the infantilism is not only of a much more conspicuous character, but that no antecedent morbid cause can be discovered. Hence in one respect it resembles sporadic cretinism, in which the infantilism is also very pronounced. But it differs in that neither the thyroid gland nor any other gland has so far been proved to be at fault. This form of infantilism has been termed *ateleiosis*.

SECTION II

The Post-Natal Disorders of Growth

I

UNDERGROWTH : DWARFISM

THE word "dwarf" is applied both to those who owe their defective stature to local deformity and to those who are not deformed, but are below the level of normal growth, say of 150 cm.

The word is used here in the latter sense only. It is now restricted, moreover, to defects of *growth* only, dwarfism due to defective development being left to the chapter on infantilism.

Dwarfism is of two main kinds, to wit :

- (1) Racial or phylogenetic, and—
- (2) Ontogenetic, or individual. In the latter case it may be either—
 - (a) Primary, or essential.
 - (b) Secondary, or symptomatic.

1. Phylogenetic or Racial Dwarfs.

The Ghurkas, Japanese, Burmese are little peoples, but are not so small as certain races living in the Philippines, in the Andaman Islands, and in Central and Southern Africa. Merely to mention them is to show how difficult it is to distinguish between dwarfism and infantilism. Possibly the Ghurkas, Japanese and southern Chinese are dwarfish only, and do not owe their stature to defective racial development, but it is quite certain that the others referred to, who will be dealt with under the head of "infantilism," represent an earlier stage of development and are phylogenetic infants.

2. Ontogenetic or Individual Dwarfs.

Defective bodily growth, affecting all parts alike and not localised (as it is in rickets, achondroplasia, and other primary disorders of

the skeleton), shades off so gradually into normal growth, on the one hand, and into infantilism on the other, that it is not easy to pitch upon actual cases of undoubted and uncomplicated dwarfism. The impairment of growth is necessarily but slight, for when pronounced it is probable that it invariably constitutes one of the signs of infantilism. Hence the condition cannot be termed a disorder, and only just comes within the limits of the definition of an abnormality. All that we can say on the subject is that there are individuals who are in every respect normal except that their stature is so far below the mean average stature of those of their own race, nation, or sex, that they may be termed dwarfs.

People so constituted resist disease organisms as well as their fellows ; are like them in respect to their intelligence and duration of life ; and, when they marry, are as capable of begetting children. Moreover, there is reason to believe that their children follow Galton's rule in being taller than their parents, so that there need be no fear of their abnormal stature being perpetuated. We ourselves have seen and measured men and women of less than 150 cm. in height who have in all other respects been strong, healthy, and well-formed on an adult standard, have passed a normal childhood, have matured in the usual way, and, in short, have shown no sign of being other than undergrown.

II

OVERGROWTH : GIGANTISM

Overgrowth may be either simple or complicated. In the simple form there is fairly uniform enlargement of all parts, but the greater the overgrowth the more likely is it to be complicated with disproportionate overgrowth or with prematurity. Simple overgrowth of pre-pubic days is termed "precocious gigantism"; simple adult gigantism is usually moderate in degree, and those affected are well proportioned, strong, live to a normal length of life, and beget children.

Introduction.

IN dealing with the subject of overgrowth of cells and of organs we recognised at least two kinds of overgrowths. In the one, or simple overgrowth, there is but little alteration in quality, the change being chiefly one of quantity, so that both structure and function may be not only unimpaired, but, if anything, increased or even exaggerated.

The other form of overgrowth consists in a qualitative change, the cells or organs undergoing increase both in number and in size, the tissue affected being also deteriorated and its function impaired.

To the first of these the name of "hypertrophy" is commonly given, though as a matter of fact, nutrition is not increased, but on the contrary is often diminished. It is also, and more accurately, termed *overgrowth* or *hyperplasia*.

The second kind is styled *degenerative hyperplasia* or *mixed overgrowth and degeneration*.

These two forms of overgrowth can again be recognised when we come to deal with the growth disorders of the whole body.

Overgrowth, Hyperplasia, or Simple Macrosomia.

Simple overgrowth of the entire body is ordinary gigantism—that is, the attainment of a height of $6\frac{1}{2}$ ft., or, say, 2 m. Some giants appear to be merely overgrown men or women. Though the long bones of their limbs are perhaps disproportionately long and their heads small, they are, on the whole, of very fair proportions; so that when we see a portrait of a giant of this description we only

know that it is the representation of a giant because we are told so, or because of the inclusion in the picture of an individual of ordinary stature, or of some article of furniture which serves to indicate the comparative size of the principal figure.

Giants of this type may be abnormal, but are not diseased. Unlike acromegalic giants, their jaws, hands and feet are not disproportionately big. They are of average intelligence, live fairly long lives, are strong, and, above all, are capable of begetting children. In short they show little, if any, evidence of degeneration.

But it must be confessed that when one of these giants dies, in all probability there will be found some disproportionate overgrowth of the pituitary body or expansion of the sella turcica, even though no obvious sign of acromegaly appeared during life. This was the case, for example, with the giant O'Byrne, whose skeleton is now in the Hunterian Museum of London.

Again, the skeleton of the lesser giant Freeman which stands by its side at first sight shows no indication of acromegaly. Moreover an inspection of the sella turcica fails to reveal any sign of its enlargement. Yet the coarse, granular appearance of some of the bones as well as the pitting of the frontal fossæ in the interior of the skull are highly suggestive of commencing acromegaly.

Yet we must claim Freeman as an example of simple overgrowth of the whole body, for although 2 m. in height during life he was of fairly just proportions, and if he showed features of a possible future acromegaly he could hardly be termed an example of that disease.

Furthermore, even when there is enlargement of the pituitary body it need not necessarily be the *cause* of the acromegaly. On the contrary it is not improbable that the local overgrowth of the pituitary organ is no more than one of the manifestations of the general overgrowth. Indeed, as we shall see later on, there is much to be said in favour of this view.

Something similar may be noticed in the case of general overgrowth of fat and its relation to the sexual organs. It is a well-known fact that defect or removal of the internal sexual glands is usually followed by excessive fatness. So also, conversely, it is equally positive that the artificial acquirement of obesity almost invariably leads to impairment of virile power or to sterility, and that one of the consequences of a drastic and effective course of fat-reducing diet is the resumption of sexual activity. This is an example of a more generalised growth disturbance acting both as cause and consequence of a local disturbance. It serves to show that there is nothing inherently improbable in the occurrence of a

similar sequence in the relations of gigantism with pituitary enlargement. Moreover, there can be no question but that there is a clinical distinction between the two forms of gigantism—simple and acromegalic.

For these and other reasons overgrowth may, at present, be separated from the gigantism of acromegaly, which will again be referred to in another chapter.

We have already seen that the overgrowth of organs is so modified by age that a particular overgrowth of one time of life may present a very different clinical picture from overgrowth of the same organ beginning at another time of life.

Far too little is known of these morbid and semi-morbid states of the whole body for a classification to be made with any pretence to finality. All that can now be attempted is to deal with certain selected cases, showing how they may be grouped in accordance with the grouping of the disorders of growth and development of cells and organs.

General Overgrowth, or Gigantism.

Group I.

Simple primary overgrowth:

- (1) Pre-pubic.
- (2) Adult.

Group II.

Complicated or correlated overgrowth, that is, general gigantism complicated with some local disorder of growth or development:

- (1) Pre-pubic.
- (2) Adult.

Group I: Simple Overgrowth.

1. Pre-pubic or precocious gigantism.—Overgrowth in foetal life, babyhood, or childhood is so often, and so closely, followed by some local derangement of growth or development that it is not always possible definitely to say which is primary, the general or the local disturbance.

A child may be born of extraordinary size, showing no evidence of disproportionate growth of any part; but subsequently, after the lapse of a few weeks or months, or perhaps years, the genital organs are found to be defective, and he comes under the head of “feminism” or “masculinism”; or, on the other hand, these same organs ripen too

soon, and the case resolves itself into one of precocious puberty. At other times the thymus and lymphatic glands enlarge, and the child dies from lymphatism or from some overgrowth or tumour of an adrenal body, ovary, or testicle.

A sequence of events of either of these descriptions admits of one of, at least, three interpretations :

(1) The local disorder may be regarded as the cause of the general, the local derangement being either latent, or patent and unobserved.

(2) The generalised overgrowth may really begin first, the local following it as a mere accentuation of the same process in a localised form.

(3) The two—the general and the local disorders—may occur independently as associated maladies, in the same way that club foot is associated with macrodactyly, or with hare-lip.

In those cases in which the general disorder precedes the local by a considerable interval the most reasonable view to take is that the second and third of these interpretations are correct, and that the local disorder is consecutive to the general. The associated disorder is not always one of an organ of growth or nutrition. Some other organ may be at fault, as in Wolff's* case, in which a disproportionately large heart was found in a giant and was not secondary to disease elsewhere. The thymus and thyroid glands were small.

In some cases there is no question as to which precedes the other, for the parents are giants. This is the case, for example, with the largest known baby, the offspring of the giants, Captain and Mrs. Bates, which weighed $23\frac{3}{4}$ lb. (10·771 kg.) and was 30 in. (0·762 m.) long at birth (see next page).

A case of uncomplicated infantile gigantism is also recorded by Cameron.† This was a female who weighed 14 lb. (6·349 kg.) at birth, 69 lb. (31·292 kg.) at the age of one year, when she was within an inch of 3 ft. (·92 m.) high, and at the age of seventeen months weighed 98 lb. (44·443 kg.). She was weaned at two, and began to walk at the same age.

We have only once had the opportunity of tracing the subsequent history of a giant child. In this case the sex organs subsequently lagged behind, so that the child's condition eventually came under the head of "feminism," and is so recorded on p. 537 (Fig. 18).

Excessive somatic growth may begin at any age before, or during,

* 'Zeitsch. für Geburt. u. Gynäk.,' Bd. xlv, 1901, S. 381.

† 'Trans. Obstet. Soc.,' vol. xviii, 1877, p. 115.

puberty, and some of these pre-pubic giants survive the stress of puberty, and afterwards come under the category of adult gigantism, such as will now be referred to.

2. Adult gigantism.—Two of the best examples of general somatic overgrowth are those of Captain and Mrs. Bates (Fig. 13).

Captain Bates was the offspring of parents of medium height, was born in Kentucky on November 9th, 1845, and at the age of sixteen enlisted in the Southern Army. He was then of average man's height, but at the close of the war in 1865 had reached his full stature of 7 ft. 2½ in. (2·20 m). "His body was well proportioned, and his weight increased until it reached 450 lb. (204 kg.)"

In 1871, when twenty-six years of age, he married Miss Swann, and died in 1882.

Miss Swann, also the child of parents of normal size, was born in Nova Scotia in 1847, and was said to be 7ft. 5in. high (2·26 m.), or 2½ in. (6 cm.) taller than Captain Bates.

There is reason to believe that these measurements were correct, if only for the reason that Captain Bates was advertised as being a little short of 8 ft. (2·48 m.) high, and Mrs. Bates as an inch or two more.

Captain and Mrs. Bates had at least two children. In a footnote to the third American edition of Dr. Playfair's 'Midwifery,' the following comment is made on the second baby:

"Probably the largest fœtus on record was that of Mrs. Captain Bates, the Nova Scotian giantess, a woman of 7 ft. 9 in., whose husband is also of gigantic build, reaching 7 ft. 7 in. in height. This child, born in Ohio, was their second, and was lost in birth, as no forceps could be procured of sufficient size to grasp the head. The fœtus weighed 23¾ lb. and was 30 in. in length. Their first infant weighed 19 lb. We have had children born in this city (Philadelphia) at maturity, and live, that weighed but one pound. The well-remembered 'Pincus baby' weighed a pound and an ounce."*

The appended portrait of this couple shows them to have been to all appearance, except in weight and stature, ordinary, commonplace people. Certainly they show no signs of acromegaly, either in their faces or upper extremities, or in any other respect.

There is one other exception, it is true, and that is the goitre to be seen in the neck of Mrs. Bates. That, however, may very well be regarded as an associated disorder, for it is not likely to have been causal. Their ordinary appearance is in keeping with their history, and with the fact that they were capable of bearing children. In

* See also the 'Medical Record,' vol. xv, 1879, p. 271. The first child weighed 18 lb. (8·163 kg.). Harris, note to third American edition.

all respects they markedly differ from acromegalic giants, who, in addition to the features special to acromegaly, are usually unintelligent, loosely knit, shambling and awkward in carriage, and sterile.

Another giant of ordinary type was the well-known Mongolian, Chang, who was said to be 2.36 m. high, and to have a sister taller than himself. We have seen him during his visit to London in



FIG. 13.—*General overgrowth or gigantism*: Captain and Mrs. Bates standing beside two people of ordinary height. They appear to be normal except in their height. They show no sign of acromegaly.

1881. He was of good intelligence, well proportioned, and without obvious signs of acromegaly. He died at Bournemouth from pulmonary phthisis at the reputed age of forty-eight.

In the records of giants, some are described as men of intelligence, enterprise, and strength, qualities which we do not look for in acromegalics. Antony Payne, of Stratton, in Cornwall, born in the beginning of the seventeenth century, was a case in point. His parents were yeomen of ordinary type, but Antony, while still a school boy, was of unusual strength and stature. At his full height

he is said to have measured 7 ft. 4 in. (2·23 m.) and was described as symmetrically formed. Fuller says, "He had a strong and acute intellect, and was also happy in his language, and of a ready wit." He became body servant to the royalist, Sir Beville Grenville. During the civil wars the latter was accompanied by his giant retainer, and on the death of Sir Beville at the battle of Lansdown, Antony Payne mounted Sir Beville's heir on his father's horse, and by his side led the troop into the fight. His portrait was painted by Sir Godfrey Kneller. He lived to a good old age, but there is apparently no statement of the date of his death.

The vicar of Payne's parish, writing in 1866,* collected some of the records of his achievements. All tend to show that he was not only tall, but broad-shouldered and muscular. Nothing, in short, is lacking in the proof of his bodily and mental soundness, but the one important exception of virility. Though vigorous and masculine in his ways, enterprising, and possessed of an unusual degree of courage, nothing is said about his marriage or children. We may, therefore, conjecture that, though in no way effeminate, he was deficient in virility.

Gigantism is so rare that the *association* with it of other growth disorders has much significance. One of the earliest cases is mentioned in the Bible. It is there said that Goliath of Gath had a brother who was a giant, and that he had a son of "great stature" who had on every hand six fingers and on every foot six toes.† An instance of the family association of gigantism with superfluous digits is also recorded by Mr. R. C. Lucas,‡ who, in giving a genealogical tree of a family liable to the latter malformation, put at the head a great-great-grandmother who possessed no deformity, but whose son was said to have been exhibited as a giant and who had a daughter with six toes on each foot. The second child of the latter had six toes on each foot and grew to be a man of over six feet in height. Several other children and grandchildren had webbed supernumerary digits and two were afflicted with hare-lips. We also read of a German giantess § who lived in the reign of Queen Anne and had neither hands nor feet. In the same book is an account of a male patient who possessed markedly feminine characters, and another instance of this association is related by Dr. Hallopeau.||

* 'All the Year Round,' vol. xvi, p. 247.

† II Samuel, xxi, 20, and I Chronicles, xx, 6.

‡ 'Guy's Hospital Reports,' S. 3, vol. xxv.

§ Gould and Pyle, 'Anomalies and Curiosities of Medicine,' p. 330.

|| 'La Semaine Médicale, 1899, No. 7, p. 53.

III

CORRELATED OVERGROWTH

Complicated overgrowth corresponds with degenerative hyperplasia of organs. The gigantism is usually more pronounced than in the simple form, life is shortened, and there is sterility.

General Overgrowth (Gigantism), Complicated with Local Disorder of Some Particular Organ: Degenerative Hyperplasia.

WE have noticed in the third part of this book that when an organ is affected with simple general overgrowth it has a special tendency to become the seat of local overgrowth (tumour) and of degeneration.

Thus the overgrown thyroid gland (parenchymatous goitre) is liable to degenerate into the still bigger fibrous organ, and to become the seat of adenomata. So also there is every reason to regard the big degenerated giant hand, with its local outgrowths of lipomata, fibromata, or angeiomata (see p. 221), as sequent to the smaller and more shapely organ affected with simple overgrowth. In the same way, overgrowth of the whole body is prone to run on into a condition which may be termed "degenerative hyperplasia." The ordinary giant child is very little removed from the normal, either in respect to size, appearance, or length of life; but as growth continues, that growth is apt to become inco-ordinate. Local outgrowths assert themselves, until the subject of the disease becomes a monster, living a very short life, and dying as the result of interference with the functions of some vital organ, or from the exhaustive process of tumour-formation.

Gigantism, like all other growth disorders, is also prone to be *associated* with local irregularities. In other words, defects or excesses of some particular part of the body may occur quite independently of the general condition. At any rate, the conjunction is not the result of cause and effect. One of the most celebrated instances of this association is the giant of Gath, to whom, with similar associations, we alluded at the end of the last chapter.

In another class of cases the general gigantism is the direct

result of the local, but it cannot be said that the reality of this relation has ever been satisfactorily established.

Hence, we distinguish at least three forms of correlated gigantism, viz. :

(1) Primary general overgrowth, leading secondarily to local overgrowth of some organ.

(2) General overgrowth, associated from the beginning with local overgrowth of an organ.

(3) Primary overgrowth of an organ, leading secondarily to general overgrowth.

In the present state of our knowledge it is impossible always to separate these three. They have therefore all been grouped together under the one heading of "general overgrowth correlated with local overgrowth."

Like simple overgrowth, the correlated variety is best divided into pre-pubic and adult.

Correlated Pre-pubic Gigantism.

The organs liable to undergo disproportionate increase during early progressive development are chiefly the thymic and lymphatic glands; the sexual organs; the adrenals; the pituitary body. Of this correlation we now give an example and further instances will appear later on.

General Gigantism Correlated with Lymphatism.

It is highly probable that lymphatic structures have some function in the inhibition of metabolism and the conservation of tissue. At any rate, babies affected with lymphatic overgrowth are often big, and are sometimes described as flabby, or of pasty complexion. It is therefore only to be expected that lymphatism should sometimes constitute the predominant note in any discord of which it forms a part. It is not improbable that the sudden death to which lymphatism gives rise affords an explanation of the early mortality of so many giant children. The following case seems to be an example :

The birth certificate of this boy is dated August 11th, 1895. He was born of average weight and height at Cwmsiflog, in the Rhymney valley of South Wales. His mother is about thirty-five years old, and both she and her husband are of ordinary stature. There is nothing in their history, or other members of their families, pertinent to the case. There is one other child, a boy, who is now three years and nine months old, and of ordinary size.

At the age of nine months D— began to grow very rapidly, without any obvious cause. There was no increase in his appetite; on the contrary, he has at no time required so much milk as his brother. He is still being suckled. His teeth did not appear until a month after he began to grow so quickly. He has had no illness



FIG. 14.—*Precocious gigantism*: Age, $13\frac{1}{2}$ months; weight, 27 kilos. The size of the baby may be gathered by comparing him with his mother, a woman of average size. There is generalised overgrowth, especially of fat. The sprinkling of coarse hair and the incipient pubic and facial hair appendages are not shown.

with the exception of some ailments which the mother calls “inward convulsions,” and which, if we understand her aright, show themselves in sudden pallor, followed by drowsiness, and want of appetite of a few hours’ duration. There have been only three such attacks,

which have occurred during the last month, and have been attributed by the doctor to "pressure of fat on the heart." The mother can give no information respecting the closure of the cranial sutures and fontanelles, nor has she noticed any other alteration in him, with the exception of the increase in size and weight, and in the loudness and tone of his voice. He began to talk about a month ago, but cannot now say more than the babyish equivalents of "father" and "mother."

His condition on October 2nd, 1896, when thirteen and a half months old, and said to be still growing, was as follows:

Cutaneous system.—On close inspection coarse dark hair can be seen sprinkled thinly over the whole of the body and limbs, with the exception of the palms and soles. The mother has only recently noticed that he is "very hairy." The hair on the upper lip and on both sides of the face, below the ears, is longer than elsewhere. The hair on the head is thick and coarse, and has already been cut on account of its length. Dentition is backward, the only teeth to be seen being the four central incisors. But the most remarkable feature of this baby is the enormous overgrowth of subcutaneous fat, which stands out from him in thick, firm folds, reminding one of the plications in the hide of a rhinoceros. Nothing but depressions are to be found in the situation of the nipples, and there is no breast substance to be felt.

His muscles are apparently of unusually good size. He is noted for his remarkable strength, and he resisted attempts to measure him with considerable vigour. A rough estimate of his muscular power was made by putting the tape in his hand and then forcibly withdrawing it. He seems as strong as the average child of eight or nine years old. The tone of the body is excellent, and the heart shows no indication of feebleness or of disease. It is impossible accurately to map out the area of thoracic resonance on account of the thickness of fat and of his restlessness; but there is apparently no dulness in the upper chest region nor any other sign of hyperplasia of the thymus. The liver and other organs are apparently normal.

His chief measurements were:

Height	91 cm.
Weight	27 kilos.
Head, circumference	52 cm.
„ greatest length	18 „
„ „ breadth	14 „
Circumference at level of nipples	71 „
„ „ umbilicus	82 „

Middle portion of total length midway between umbilicus and pubes.

Intelligence.—Though the size of the head is equal to that of an adult, yet the child is intellectually backward for his age. He is bright and lively and good tempered, but his manner is that of an intelligent infant of from eight to ten months. He cannot sit upright without support, and has not yet learned to be clean in his habits. He sleeps well at night, and also for about two hours in the day.

Sexual system.—On the other hand, as regards his genital organs he is in advance of his age, for though the penis is retracted and apparently small, it is in reality only concealed by the thickness of the fat in its neighbourhood, and is, we think, decidedly larger than is usual for so young a child. The scrotum also is as rugose as that of a youth at puberty, but, so far as can be judged, the testicles are not unusually large. The hair on the pubes is not conspicuous, but is undoubtedly longer than elsewhere, and reminds us of the appearance in a boy just before the onset of puberty.

Event.—Six weeks after we saw this baby we heard that he had died a fortnight before, at the age of fourteen and a half months. He had not notably increased in size nor altered in other ways save that the “inward convulsions” had increased in frequency. They were apparently of the nature of the syncopal attacks which take place in the status lymphaticus, and, like them, ultimately proved fatal. They lasted a few seconds, were attended by increase of pallor, but were not associated with eclampsia. No *post-mortem* examination was allowed. This case is, therefore, unsatisfactory, for we know nothing of the state of the supra-renal bodies and of other internal organs. It may safely be regarded as one of infantile gigantism, complicated with lymphatism, but there may have been other disorders.

A water-colour portrait of a still more remarkable case of complicated gigantism was given to us by Colonel McCleod, but we regret to say that this was subsequently lost in the post. The picture was of a high caste Hindu lady in a sitting position, and carrying on her left arm an enormous infant of less than a year in age. This monster child was excessively fat, but not after the manner usual with babies, for the fat was not so much rounded off as disposed in thick segments and plates separated from one another by deep grooves. It was breast-fed, and was seen by Colonel McCleod only once, for though the mother was requested to come again nothing more was heard of her.

A celebrated case of similar kind was that of Thomas Hills Everitt, described by Wilson* and other writers of the curious at the end of the eighteenth and beginning of the nineteenth centuries. The account given of this child is summarised as follows :

This prodigious child—an extraordinary instance of the sudden and rapid increase of the human body—was born on February 7th, 1779. “Neither of the parents was remarkable for either size or stature. Thomas was their fifth child, and the eldest of the three living in 1780 was twelve years old, and rather small for his age ; but the paternal grandfather was of a size larger than ordinary. They had another son of uncommon size, who died with measles in January, 1774, at the age of fifteen months.

“Thomas was not remarkably large when born, but when six weeks old began to grow apace, and attained a most extraordinary size. At the age of nine months and two weeks his dimensions were taken by Mr. Sherwen, an ingenious surgeon, residing at Enfield, and compared with those of a lusty boy of seven years old. The result was as follows :

	Dimensions of the (giant) child. Inches.	Dimensions of the normal boy. Inches.
“ Girth round the wrist	$6\frac{3}{4}$	$4\frac{3}{4}$
„ above the elbow	$8\frac{1}{2}$	$6\frac{1}{4}$
„ of the leg near the ankle	$9\frac{3}{4}$	$6\frac{1}{4}$
„ of the calf of the leg	12	9
„ round the thigh	18	$12\frac{3}{4}$
„ round the small of the back	24	22
„ under the arm-pits and across the breast	$22\frac{3}{4}$	24

“Mr. Sherwen, who, in November, 1779, transmitted the above account to Mr. Planta, secretary of the Royal Society, added that he should have been glad to have given the solid contents of animal substance, but was prevented by the vulgar prejudice entertained by the mother against weighing children. He could therefore only say that, when she exposed to view his legs, thighs, and broad back it was impossible to be impressed with any other idea than that of seeing a young giant. His weight was, however, guessed at 9 stone, and his height at this period was 3 ft. $1\frac{1}{4}$ in.”

“He was well-proportioned all over, and subsisted entirely on the breast. His countenance was comely, but had rather more expres-

* ‘Wonderful Characters,’ p. 430.

sion than is usual at his age, and was exceedingly pleasing from his being uncommonly good-tempered. He had very fine hair, pure skin, free from any blemish, was extremely lively, and had a bright, clear eye. His head was rather smaller in proportion than his other parts." His death took place about the middle of 1780, before he had attained the age of eighteen months.

IV

OBESITY

Obesity shades off into lipomatosis and lipomata. Obesity is correlated with sterility, muscular overgrowth, etc. It is a variation, major or minor, and a disorder of *growth*, as distinguished from development and nutrition. Obesity as a *major variation* is met with in very pronounced forms. It is often hereditary, has no cause, is associated with muscular and sexual anomalies, diabetes, infantilism, and genius, and is incurable. As a *minor variation* it is not hereditary, is due to a variety of causes, is, as a rule, less pronounced, and is associated with many disorders. There are two types—the plethoric and chlorotic. It is curable by regulation of diet and by other means.

Introduction.

No disorder of the body is more difficult to classify satisfactorily than obesity. This difficulty arises mainly from the fact that, generally speaking, it is not one pathological condition, but several. In one case the over-fatness seems to be merely an excessive growth of adipose tissue, or the fat organ, much as the strength of the strong man is due to excessive growth of muscle; in a second case the obesity is the result of changes in the sex-glands; in a third it consists in a persistence of a condition normal in babyhood; and in a fourth it is an indication of defective action of the thyroid gland. Moreover, it is not possible definitely to classify obesity in accordance with these pathological divisions, for they are so bound up together by ties of correlation that it is often very difficult to disentangle them. Indeed in certain cases there is such a mixture of these anomalies that we are quite unable to say which comes first and is responsible for the others. Fat, as an organ, comes into such close association with the skin, on the one hand, and with underlying muscles on the other, that all three tissues must needs be closely associated in disease. Moreover, while fat exists elsewhere, by far the most important collection is that which covers the body like a blanket. This, therefore, must be regarded as the predominant element in some cases of obesity.

At the same time the fat of one part of the body has such intimate relations with the fat of another part, that when that situated beneath

the skin is either increased or depleted the fat elsewhere usually shares in the process. This is by no means always the case, for in some obese patients the increase in fat is chiefly subcutaneous, others are troubled with fatty abdomens, and yet others have their obesity distributed irregularly in lumps. Obesity of this last kind must be distinguished from the diffuse lipomata which hang about the neck or at the junction of the limbs with the trunk. These are either innocent tumours, and therefore of single cell origin, or are intermediate between lipomata and that generalised overgrowth of fat as an organ which is obesity.

Some cases of over-fatness in young life arise in babyhood. This *precocious obesity* consists in the perpetuation of the fatness characteristic of that time of life. It is, in truth, a form of infantilism, for though the growth of the muscles, and of the skeleton, continues on to an adult type, the physiognomy often retains much of its childish character; the limbs are sometimes uncommonly short, the sex organs remain undeveloped, and, as we have said, the fatness and roundness of the body and limbs are eminently childish.

Many obese individuals remind us strongly of overgrown children. This likeness has, in fact, been taken advantage of by music-hall managers, who sometimes dress fat men or fat women in boys' or girls' clothes, as the case may be, and put them on the stage to play the parts of burlesque children. We have a photograph of a woman so dressed, and she looks exactly like a girl still in the short frock and socks stage of existence, her physiognomy and proportions are so thoroughly in keeping with her dress. She is represented as crying, and a little ateleiotic dwarf is about to wipe her eyes with a handkerchief, having climbed up with the help of a ladder planted against her shoulders.

Now there is very little margin between a mere negative absence of sex and positive hermaphroditism, or, at any rate, feminism. It is one of the customs of the body that removal or failure of the sexual organs should be attended with increase of fat. This inverse relation between fat and sex is so close that it is also maintained when conditions are reversed, and the disorder is in the first place not of the sexual but of the adipose system.

When these associated disorders occur the change is never localised nor abrupt, but is widespread, losing itself gradually in ever-lessening changes in associated organs. Obesity, therefore, not only brings about sterility, but the secondary organs of sex are also implicated. The facial hair, the physiognomy, voice, temperament, habit of life, all are affected more or less. Hence the aggressively fat man is

prone to have an undeveloped type of face. It is short and flat, the nose being small and retreating, the facial hair deficient. He is often a little timid, his voice is as a rule tenor, and he shows other qualities indicative of a feminine bias.

What is true in these respects of over-fatness is applicable, in principle, to over-thinness. The lean man is not only spare of fat, but of muscle, so that he tends to gauntness and angularity of outline, and it is proverbial that his reproductive proclivities are unusually keen.

So also very fat women are prone to grow facial hair and to assume a more masculine appearance. Gould and Pyle* give a likeness of an extremely fat woman with a well-developed beard.

Another organ at the bottom of many cases of adiposity is the thyroid gland. The degeneration of this gland is, no doubt, the cause of much of the obesity of middle age. But there is reason to believe that it is not only the direct cause of this complaint, but acts also to some extent by correlation. At any rate in some cases of obesity, definitely due to other causes than thyroid inadequacy, treatment by means of thyroidin or thyroid extracts is sometimes followed by reduction in weight. This seems to indicate that the adiposity has itself had an inhibitory effect upon the thyroid gland. It is in accordance with the known facts of correlation to infer that not only does thyroid inadequacy favour fatness, but that fatness tends to lessen the action of the thyroid gland.

Another aspect of obesity which demands attention is the way in which it is *associated* with yet other morbid and semi-morbid conditions. Thus we find not only *infantilism*, *sex negativism*, *feminism*, *myxœdema*, but *overgrowth of the muscular system*, *certain anomalies of the skin appendages*, all or singly as accompaniments of overgrowth of fat.

The genesis of these secondary disorders is the natural consequence of the normal correlation of the muscular, cutaneous, and sexual systems with the adipose system. The man who increases in substance by 4 st (25 kg.) has attached to himself a burden equal in weight to two bicycles, and this load must be carried by him wherever he goes. Were his muscles to remain as they were before this incubus of flesh was laid upon them, it is probable that they would break down under the intolerable strain of the constant exertion. But, as a matter of fact, they increase by imperceptible degrees, in keeping with the increase in weight. So closely associated are strength and fatness that the considerate German never

* 'Anomalies and Curiosities of Medicine,' p. 360.

uses the word "fat" in describing a fat man, and even "thick" is dropping out of use among the polite. The objectionable fat is now completely ignored, attention being diverted to the muscles by the use of the epithet "strong." It is recognised that a fat man is also a strong man.

No organ of the body is, perhaps, more implicated in obesity than the skin. It is true that the skin of some very fat people seems to share very little in the overgrowth of the adipose tissue. It looks so tense and shiny as to suggest that it is merely stretched over the underlying fat. But, as a rule, it is evident that the skin has perfectly accommodated itself to the altered circumstances, and now and again it may even be loose and hang about the body and limbs like an ill-fitting garment. In the last cases the overgrowth of fat is associated with such inordinate overgrowth of skin that the skin hyperplasia is actually in excess of the fat hyperplasia. This skin redundancy may be observed in some very fat people, but is especially noticeable in that peculiar form of obesity termed "*adiposis dolorosa*." Indeed, in some cases of this disease, the loose, flopping integuments hanging in an untidy way from the arms or abdomen, or dependant round the trunk in overlapping folds, constitute a very conspicuous disfigurement.

The Relation of Nutrition to Obesity.

Obesity furnishes a good example of the triple sense in which the word "nutrition" is used. The fat individual is often referred to by nice people as "well-nourished," this epithet being the expression of the general opinion that excessive fatness is mainly the outcome of over-assimilation of food. On the other hand, the word "nutrition" in its relation to obesity is used in a widely different, almost opposite, sense. Thus the beer drinker, growing excessively fat, succumbs to pneumonia, not because his trophic or nutritive power is increased, but because it is diminished.

So also one of the concomitants of obesity is diabetes, which is commonly regarded as a disease of "nutrition." Moreover, as Sir James Paget long ago pointed out, the obese, because of their sensitiveness to shocks and their general vulnerability, are peculiarly "bad subjects" for operations.

Evidently the word "nutrition" is applied indiscriminately to growth, to alimentation, and to resisting powers. In health it is connected with both growth and development by inseparable ties, but these ties are more or less loosened in disease.

A state of good nutrition may assist growth, but is not itself growth. So also defective nutrition may facilitate degeneration. The fat man, therefore, who is so often termed "well nourished," may to some extent owe his plumpness to nutrition, or the reverse; or, on the other hand, nutrition may primarily have very little to do with it. It is, then, in reality, in the first place and mainly an affair of growth or of degeneration.

Obesity as a Variation.

One important generalisation in respect of this subject of obesity is obvious, even to the most casual observer, and that is that fatness and leanness are derived in more than one way. It might almost be said that some people are born fat; others acquire fatness, while others, like Strasburg geese, have fatness thrust upon them. It is certainly a fact that some grow fat almost spontaneously, and, perhaps, even in spite of desperate efforts to remain thin. Others evidently owe their obesity largely to inordinate eating, assisted, it may be, by laziness and over-indulgence in alcoholic liquors; and some who belong to this class can only be fattened by gross and deliberate over-feeding.

All this points to the conclusion that obesity and emaciation are of two kinds, the one being a *major* and the other a *minor* variation. But before we can enter upon these subjects we have first to determine as to which description of disorder fatness and thinness belong. Are they, in the beginning, the result of nutritive changes, or of growth, or of development?

Putting the question of nutrition aside for the present they are seemingly, as a rule, disorders of *growth* rather than of development. But whereas the obesity of early life is the result of sheer exuberance of function on the part of the fat-cells, and has its springs, therefore, in progressive development, that which sets in after middle age seems to derive its impulse from degeneration. It is apparently a true overgrowth resulting from that loosening of restraint which all organs and tissues undergo when they begin to degenerate; but the overgrowth predominates to such an extent that the degeneration is thrown into the background, taking a very subordinate position.

Degeneration would lead either to fatness or thinness. When slight it would tend to excessive growth, as we have just seen. But when the fat-cell undergoes the rapid deterioration, with proliferation, which is implied in active senile degeneration, its

function must necessarily suffer. Instead of secreting fat, it undergoes fatty decay—a very different process—and the decayed protoplasm is absorbed, leaving at last a small round inert cell, useless as a fat producer, and probably combining with fibroblasts and lymphocytes to form new fibrous tissue.

Obesity as a Discontinuous or Major Variation.

We regard it as an axiom that the earlier in life a developmental or growth disorder originates the more likely are associated organs to be implicated. Major variations, therefore, which tend to occur in the young, are not only far more emphatic in themselves than minor variations, but are associated with more pronounced disorders. So true is this that it is often difficult, or it may be impossible, to say which is the primary element in a given case of obesity, or whether there is not more than one variation occurring at the same time.

For example, we give on p. 537 a few details of a case of post-natal hermaphroditism. But the lad is evidently obese, and it is by no means unlikely that this was the dominating factor, the infantile development of the sexual organs being secondary. This seems to be the more likely, inasmuch as he first attracted attention when an infant by his enormous size, so that in the photograph which we have taken of him at that time of life, he appears to be affected with infantile obesity. Indeed, he was actually so referred to by Mr. Yorke Davis in a letter to the 'Lancet.' The fact that the obesity appeared so early in life, and was so extreme, makes it highly probable that it was the predominant element, and that the sexual defect was present by mere force of association. The state of this boy was first one of infantilism, but later on it might quite as accurately be termed one of feminism, and is therefore presently to be described under that heading.

In other cases, where there is an unusual degree of physical strength, it may seem difficult to come to a conclusion as to whether overgrowth of fat or overgrowth of muscle comes first in order of precedence. But in reality it is highly improbable that the obesity is secondary, because, though under normal circumstances increase of muscle is requisite when there is increase of fat, it does not follow that more fat is required when the primary excess is of muscle. Indeed, it is evident that while extra muscle is required to carry extra fat, fat can be nothing but a clog to the strong, impeding, and not facilitating, the action of their muscles. It is therefore

pretty safe to say that in every case of obesity (of discontinuous origin) with muscular overgrowth the obesity is primary, and the bigness of muscle secondary, however well-balanced the co-ordination may be.

All the chief features commonly met with in obesity as a major variation are illustrated in the following cases.

These occurred in a New Zealand family which for a time was touring in this country as a public exhibit. This family consisted of father, mother, and seven children. The parents and five of the children seemed to be normal individuals. At any rate we could speak for all except two of the children, who happened not to be present at the time of our visit. We saw a portrait group of the whole family, and all looked of ordinary height and weight except two, and these two, a boy and a girl, were so conspicuously unlike the rest of the family gathered about them that they at once monopolised attention. Upon subsequent examination it turned out that of these two, one, a boy of 11 years, is 1·7 m. high, has a chest circumference of 1·4 m., and is said to be over 139·5 kg. in weight. The other, a girl of 15 years, said to weigh 107·8 kg., is 7·5 cm. shorter than her brother.

Here we have a tremendous contrast between the two obese individuals and the rest of their family, such as is characteristic of major variations.

Though enormously stout, the fat was mainly of the subcutaneous tissue. So far as could be judged there was no disproportionate fatness anywhere. The fat was so distributed as to be carried to best advantage, and in neither case was the abdomen pendulous. In only one respect did there seem to be any irregularity in the disposal of the fat, and that was in the breasts of the boy, which were very big and dependent. This was undoubtedly an opposite sex feature (gynæcomastia). Though there seemed to be no actual breast-tissue present the nipples were, for a boy, very well-defined. He was not somnolent either in manner or habits, but looked healthy, alert, and intelligent, and enjoyed a frolic, though his gambols were like the gambols of a hippopotamus.

His muscles were obviously of large size, notwithstanding that their outlines were entirely hidden by the thick covering of blubber. Though living an active life, and capable of walking some six miles or more, he was seldom tired, and as a rule seemed as fresh at the end of the day as at the beginning. He could easily lift his sister, notwithstanding the awkwardness of the operation.

The adaptation did not stop at the muscular system, but had also

involved the bones. At any rate, his breadth of chest and hip seemed not to be wholly due to thickness of fat, and the bones, where capable of being felt, as at the wrists, were apparently bigger than usual. Moreover, the growth of the bones was considerably in advance of that usual to his age, for his height was no less than 39·5 cm. more than the normal height. He was, therefore, not only an example of precocious obesity but of precocious gigantism.

In regard to the reproductive apparatus, it is remarkable that while in the case of the boy it was of infantile development, and sexual hair was absent, the girl seemed to be normal in these respects. She began menstruating at thirteen, and had continued to menstruate at intervals of four weeks ever since. This want of correspondence between brother and sister in this one particular alone serves to illustrate the fact that the rule of association of correlated diseases is a rule only and not a law. It is therefore liable to those occasional exceptions which both break and prove all rules.

No case of obesity has, perhaps, attracted more attention than that of the celebrated Daniel Lambert.

The following particulars, taken from 'All the Year Round,'* will serve to show how little the fatness may be the product of causes, and how complete may be the muscular correlation :

Daniel Lambert is said to have been both temperate and active. He was a small and careful eater. "He never drank anything but water, though being a fine tenor singer and very fond of society he was exposed to great temptation. He slept less than other men, and could always wake within five minutes of any time he wished. He was so active that even when he had grown to a big man he would kick to the height of seven feet, and when thirty-two stone weight he walked from London to Woolwich with less fatigue than several middle-aged men. In his youth he was passionately fond of field sports, and always retained his taste for them. It is said that 'he would carry five hundredweight with ease.'

"He seemed to have been very little inconvenienced or oppressed by his immense bulk.

"Lambert died without any visible disorder, and quite suddenly, in his fortieth year. At that time he weighed nearly fifty-three stones (366 kg.)."

Associations.—Obesity as a major variation is not only associated with muscular and sexual anomalies, and with diabetes, but with many others. Among these are the following, namely :

* Vol. iii, 1860, p. 480.

Obesity associated with *general infantilism*. A case of this description is figured by Drs. Gould and Pyle.* Dr. Guthrie† also records a case, but of less pronounced type.

Obesity associated with *lymphatism* and *infantile gigantism* and *sexual overgrowth*. Details of a case have been given on p. 496. The association with sexual precocity is remarkable, seeing that it is the opposite condition which is to be expected. Probably in these cases the dominating factor is not the obesity, but either the sexual precocity or the general overgrowth, the lymphatism determining the obesity.

So, also, when corpulency and *hirsuties*‡ go together we shall probably be right in regarding the hairiness as a sex character, though it is not necessarily associated with premature development of the sex organs.

Suprarenal tumours are of frequent occurrence. Dr. Guthrie§ found that out of ten cases of precocious obesity hypernephroma was present in eight and in one no *post mortem* examination was held. There may or may not be premature sex development as well (see p. 528).

We have seen a case of Dr. C. Rolleston's of juvenile obesity in a boy with Friedreich's ataxia. Several children in the family were affected with the ataxia, but only one other was obese. Neither of the parents was over-fat.

As a rule the effect of obesity is apparently to increase rather than to diminish height. This is especially true of pre-pubic obesity. It is probably the result of correlation, the extra weight implied in over-fatness leading first to growth of muscle, and this, again, to an associated growth of bone. Most of the precociously fat children met with in variety shows are therefore prematurely broad and tall. Generally this disproportion of growth stops at puberty, so that the infantile giant ceases to be a giant so far as height is concerned, and often, indeed, becomes less gigantic in regard to the deposit of fat.

As a rare event obesity is associated with *adult gigantism*. Perhaps the most pronounced instance of this combination is described by Williams.||

Another association, which cannot be passed over, is that of *genius* with obesity. Agesilas, Haller, and probably Samuel Johnson, Renan,

* 'Anomalies and Curiosities of Medicine,' p. 341.

† 'The Polyclinic,' 1906, p. 21.

‡ 'Anomalies and Curiosities of Medicine,' p. 360.

§ 'Brit. Med. Journ.,' 1907, vol. ii, p. 748.

|| 'Medical Press and Circular,' vol. ii, 1888, p. 557.

and Gibbon are examples of this combination. In our own profession Simpson and Lawson Tait were men of exceptional gifts of initiative and of executive ability, and these qualities were combined with a type of corpulency which could hardly have been otherwise than inborn.

Moreover we can all call to mind a great modern writer, capable of enacting the part of Falstaff from the physical standpoint, who joins with his greatness of body such a surprising agility and originality of mind, of somewhat limited range, as to come within the definition of genius.

The following is a remarkable case (under the care of Dr. Abram) of obesity associated with sexual, mental, sensory, and motor defects.

The patient is a boy, aged 8 years and 4 months, whose height is 3 ft. 9 $\frac{3}{4}$ in. (116 cm.), and weight 61 lb. (27.6 kg.)

The first thing that was noticed amiss was that he was backward in walking and talking. He gradually picked up a few fragments of words, but even now his vocabulary is so limited that he uses hardly anything but monosyllables, and when asked to repeat a sentence usually jerks out the concluding word alone.

There is muscular weakness in every direction. He is quite unable to walk, and can only just support himself erect. Until a year ago he could not be trusted in a chair unsupported. His mouth is habitually open, but this may partly be due to the fact that his tonsils are moderately enlarged. He still slobbers a little at times, but has greatly improved in this respect during the past year. His grasp and the push of his feet, in the act of extension, are very feeble. Up to two years ago there was incontinence of urine and fæces, and he still wets his clothes occasionally.

His face has a vacant, expressionless appearance, and at intervals he distorts his facial muscles in an inco-ordinate, meaningless way.

Examination of his nervous system reveals a remarkable diminution of the sense of pain. This is universal and uniform, so that pins may be stuck into the skin of any part without comment, though there is a slight start of the underlying muscles. At the same time the mother is sure that he has tender feet. He cannot bear to have his nails cut, and cries when that operation is attempted.

His intelligence is undoubtedly defective, and it is difficult to get his attention for a few seconds while a photograph is being taken. The action of the pupils is normal, the knee-jerks are brisk, and there is an extensor toe reflex.

Neither of the testes can be felt, either in the scrotum or along the canal.

He did not begin to grow fat until a little more than two years ago, but of late he has rapidly increased in size.

The salient features of this case are the combination of extreme muscular hypotonus and conspicuous hypoesthesia, combined with sexual defect and obesity in a boy of normal height.

Excessive fatness as a major variation is naturally best exemplified when it occurs in infancy, for it then follows the rule that the earlier in life an anomaly of growth or development appears the greater is its degree. But as a matter of fact, obesity as a major variation can appear at any age. We meet with it occasionally in girls at puberty or thereabout, and it is peculiarly prone to crop up at the menopause. But, after puberty, the later in life it begins the less complete is the muscular or other associated semi-morbid condition by which it is accompanied.

Obesity as a Continuous, or Minor, Variation.

Heredity is thought to play a very important part in the production of excessive fatness, and by way of evidence statistics have been brought forward to show that in a very large percentage of cases the complaint is to be met with in more than one member of the same family. But there are so many circumstances which detract from the value of these figures that in the end they must be whittled down to far more slender proportions. Thus, first of all, difficulties must arise from the fact that we cannot say precisely where mere fatness ends and obesity begins. Some doctors and some patients will see an abnormal excess where others see nothing but ordinary fatness. Then, again, fatness is so common and is due to so many different causes that we can hardly account for its occurrence in excess in different members of the same family on the score of heredity unless there be other reasons for so doing. Moreover, we have to distinguish between the heredity of obesity and the heredity of some condition which is not itself obesity, but leads on to obesity, such as susceptibility to alcohol, or to gluttony, or some other factor capable of inducing the excess in people who would not otherwise acquire it.

Perhaps of no malady have we been more sure in regard to heredity than cancer, yet now, thanks to the investigations of Prof. Karl Pearson, we are bound to come to the conclusion that its transmission takes place so rarely that it is practically not heritable. On the other hand, in the very few exceptions met with, the heredity

is so emphatic that no room is left for doubt. So is it, in all probability, with obesity. If the records should be handed to some statistical expert we should not be surprised to find that much the same can be said in this respect of the heredity of obesity as of cancer.

Causes.—The form of obesity just discussed is easy to deal with from the point of view of causation, seeing that it has no cause; but the obesity we are now concerned with suffers from a superabundance of causes. But all these causes may be grouped together into those which (1) directly increase the formation of fat and those which (2) do so indirectly by removing some inhibitory influence.

Among direct causes the chief is over-assimilation of food, leading to increased action of the fat-cells. Excessive food supply may be relative only, as where the intake of food is not compensated for by the exercise taken.

Alcohol, when sufficiently diluted, apparently fattens by reason of its inhibitory effect upon metabolism, and partly, perhaps, because of the increased flow of nutrient material which the dilated vessels bring to the tissues.

All the ordinary causes of over-fatness act with most effect at certain physiological epochs. Thus no one who has had to do with the fattening of consumptives in the old days of over-feeding can have failed to notice how much easier it was to add to the weight in the autumn than in the spring-time. The normal seasonal variation in weight, which is at its ebb in the late winter and early spring and is stationary in summer, begins to rise as the cold weather comes on in preparation for the scarcity of the winter. Advantage is taken of this autumnal tide by those members of the animal kingdom to whom it is of importance that they should lay up stores of fat. Hence the hibernating bear, the bat, and the emaciated human being all rejoice in an easy access of weight at this time of the year. So also the man who is feeding too grossly sometimes dates the onset of his obesity from that period.

Another *seasonal variation* responsible for obesity is that which seems to have its origin, not in the periodicity of the sun, but of the moon. The pre-mensal rise of nutrition, most noticeable in women, is too slight to be of any importance in the production of obesity, but when magnified, as in pregnancy, it becomes of very great importance, for many a too-fat woman can look back to this period as the beginning of her trouble.

Of still greater consequence are the great epochs, or *climacterics*. Infantile corpulence may begin with the chubbiness of infancy. As

a rule the over-fat baby loses his excess of tissue with his babyhood in the accelerated metabolism of childhood. But occasionally true childish obesity traced to over-feeding in babyhood is carried on into the next stage.

The awakening of the reproductive apparatus at puberty often mitigates or puts an end to childish obesity, partly by the accelerated growth of muscles and skeleton and partly by the increased metabolism of this period. But sometimes in normal individuals, instead of having a levelling effect, the spurt of growth and development eventually results in an unseemly preponderance of some organs over others. This inco-ordination accounts for many cases of over-fatness of the chlorotic type. The lack of co-ordination is shown in hypoplasia of the heart and arteries, in hypoplasia (sometimes hyperplasia) of the uterus, in relative or actual overgrowth of the blood (chlorosis), and occasionally in excessive fatness. Chlorosis gives rise to obesity apparently in part by lowering metabolism, in part by causing deficient oxygenation of the tissues, and in part by the enforced sedentariness of life which the chlorosis entails. But it is not possible to say how much of the increase in weight of chlorotic girls is due to obesity and how much to mere distension of the tissues from increase in the quantity of blood.

Retrogressive or *degenerative corpulency* may appear at any time of declining development, but is especially apt to come on at the menopause. It may then proceed from (1) lack of thyroid secretion due to over-degeneration of the thyroid gland; from (2) sexual correlation, whereby the normal increase of fat which is associated with the loss of sexual function becomes exaggerated into right-down corpulency; or, lastly, it may be directly produced and result to a very large extent from the (3) lack of exercise induced by the lethargy incidental to this time of life.

The increase of fat and the other phenomena which result from defective action of the sex-glands are usually imputed to the deficiency or absence of a hypothetical secretion from the ovaries or testes. Reasons have already been given for looking upon them as the outcome of correlation, and correlation alone. Nothing is, perhaps, more in favour of this view than the fact that not only does fatness as a sex character result from incompetence of the sex organs, but sexual incompetence arises out of fatness. Though this is shown more sensationally when the obesity is a major variation, it is perhaps more convincingly demonstrated when the obesity is a minor variation. We then see that men or women who fatten rapidly usually experience a conspicuous falling-off in sexual vigour.

And if, perchance, by means of treatment, they are successful in reducing their weight to its normal level, they again become virile or fertile. That this is an actual sequence and is not mere fancy is proved by the return in some cases of sexual indifference with each lapse into obesity, and, above all, by the effect of these fluctuations upon menstruation.

Origin.—The above are the causes of fatness, but not necessarily of obesity. Fatness must reach to a certain pitch of perfection before it can be said to be abnormal, and to constitute obesity. Moreover, it is doubtful if sheer over-eating will alone produce true obesity. It is required that there should be, in addition, an inborn disposition to accumulate fat in excess. In short, obesity of the acquired type can only occur as a minor variation.

Types.—Two types are recognised—the chlorotic and the plethoric. The *chlorotic* occurs usually in females, and is the pale, flabby fatness of puberty, or *embonpoint* of the menopause. The *plethoric*, on the contrary, is associated with great muscular vigour. The John Bull of Rowlandson with the coarse, florid, pimply face, corpulent, sturdy body, and aggressive, hot-tempered manner, is an excellent example.

Distinguishing Features of Obesity as a Minor Variation.

This form of obesity is, as we have just seen, invariably an acquisition.

It is never inherited. By this it is not meant that the disorder cannot take place in more than one member of the same family, but that where it does so occur it is the result of coincidence, or is the inheritance, not of the obesity itself, but of some predisposing factor.

Obesity of this pattern is, as a rule, not so pronounced as is that due to major variation. It is also far more likely to be of irregular distribution, and generally the deposit of fat is much thicker upon the abdomen than elsewhere.

Though less in degree it is more truly an affliction than is the other variety, because there is less associated increase in the size of the muscles. At the same time *correlation* does come into play, so that we can often see that the load of fat is carried with an exaggerated uprightness of figure and with a firmness of tread not entirely to be accounted for by *avoirdu pois*, nor by the necessary adjustment to a centre of gravity seated more forward than usual.

It is known that some nations thoroughly appreciate the fact

that increase of fat involves increase of muscle. Among the Japanese, for example, a great wrestler is a fat man, and in training it is regarded as of the first importance that he should eat enormous quantities of fatty foods, in order to keep himself at the highest possible level of adiposity. Doubtless he and his advisers also have in view the advantages of weight and of slipperiness, but in a form of sport in which sheer strength is most required it is not likely that the practical Japanese would sacrifice this for lesser considerations.

On the other hand, muscular correlation is sometimes very defective, especially when fatness sets in after middle age, when the muscular system is no longer able to rise to the occasion. A vicious circle is often established. The tired muscles insist upon rest, but more rest means more fat, and so the inadequacy of the muscles is still further increased.

A disorder of nutrition which is frequently associated with corpulency is *gout* (to the extent of 43 per cent. in a series of 543 cases, according to Dr. Anders).*

Diabetes is, as we have seen, an occasional concomitant. The obese are also prone to fail in their *capacity for resisting micro-organisms*, so that they are liable to succumb to carbuncles, pneumonia, or to other bacterial invasion.

Arterial sclerosis is also frequently met with. But one of the most interesting of these associated disorders is overgrowth of the red-blood system. The hyperplasia may result in an increase of erythrocytes to 6,800,000† or more per c.mm. This *polycythæmia* occurs in the plethoric type of obesity. The chlorotic type is associated with overgrowth of all the constituents of the blood, constituting *chlorosis*.

We also meet with *granular kidneys*, often induced, no doubt, by the alcohol which is responsible for the obesity. Dr. Labbe‡ holds that "sclerous nephritis" is extremely "frequent in the obese." Indeed, it is the rule in the gouty obese. He is evidently referring to the obesity of adult life, and not to juvenile obesity.

Consequences and Treatment.

Obesity as a major variation, seeing that it exists independent of circumstances, may be regarded as incurable.

* Osler and McCrae, 'System of Medicine,' p. 845.

† *Ibid.*, p. 850.

‡ 'Le Monde Médical,' 1908, p. 375

Unfortunately, we cannot always distinguish between the two kinds. Though we recognise their essential differences in a general way, isolated cases occur which baffle attempts at classification.

We should expect the major kind to be the less dangerous of the two, for an obese individual who owes his fatness largely to intemperance in eating or drinking has necessarily lowered his vitality in more than one way.

This is not the place elaborately to go into the question of diet. All that need be said is that whatever system is adopted its action must be regarded as equivalent to that of a mild starvation. Bulky vegetables of low food value may be given, and the body may be deceived by soups, beef-tea, broth, or other watery solutions of nitrogenous waste into an impression that food is being swallowed, but the common articles of real value, such as bread and milk, potatoes, and meat, must be doled out in ineffective dribblets. Above all it is necessary to be parsimonious with carbohydrates, and not to fall into the common error of supposing that bread dried before the fire as toast is of inferior food value to bread cut fresh from the loaf.

In the treatment of obesity dieting should go hand-in-hand with other measures. It must be regarded as good tactics to begin treatment in spring or early summer, when it will fall into step with the natural wave of fat loss which begins at that time. Moreover, exercise is of capital importance, seeing that increase of muscle not only enables the fat to be carried more easily, but probably by correlation actually assists in its reduction.

SECTION III

The Post-Natal Disorders of Sex

Over- and Under-Development of Sex; Masculinism; Feminism

I

INTRODUCTION

Civilisation promotes sex specialism on the one hand and neutrality on the other.

Over-development and under-development of sex occasionally occur to such degrees as to become morbid and constitute disease. **Masculinism and feminism** are equivalent to post-natal hermaphrodisism. They are liable to be associated with other developmental disorders, and occur either in very marked forms as major variations or in less pronounced degrees as minor variations. They may affect either individuals or races.

Nothing seems to be more certain than that the possession of strongly marked sexuality must be considered as one of the most important indications of an advanced state of development. In woman this arises as a necessary result of her position as child-bearer. The advanced femininity of the highly civilised female is necessarily both cause and consequence of the long period of helplessness of her offspring. A virtuous circle is formed, the antithesis of one of Dr. Hurry's vicious circles, in which the "anabolism" of the female, the helplessness of her child, and the evolutionary status of the mother constitute the circumference. But one other factor is requisite for the completion of such a circle as we now contemplate, and that is the centre. This is necessary in order to give cohesion and stability, for, as a matter of fact, our circle is a wheel, and the feminine wheel of life is entirely dependent upon the continued existence and support of the katabolic or masculine element round which it revolves.

The tendency of modern civilisation is to act upon sex, and

especially female sex, in two contrary directions, one of which leads to an increase of sex and the other to a decrease.

An important feature of modern life is division of labour. Specialism, in short, exists to such an extent that in our own profession we have specialists who spend busy lives in the study and treatment of the diseases supposed to depend upon a single constituent of the urine. Such being the case, it is hardly to be wondered that the primitive specialism of child-bearing, the one paramount function of the womb-man or woman, should also continue to advance in a similar manner, as well as all that pertains to it.

Immense strides have been taken in the post-natal care of the child since the days when the woman was not only the child-bearer and child-breeder, but the tiller of the soil, the bearer of burdens, and the performer of the multifarious duties of the drudge. One cause and consequence of this lack of specialisation was that the primitive woman was not only devoid of the graces and refinements of femininity, but showed little of that bodily configuration which we associate with the female sex. Travellers among those living races which most nearly correspond with primitive man refer not only to the lack of beauty and other attractive qualities of the women, but to their harsh, angular outlines, to their greater growth of muscle and bone, to their narrowness of pelvis, and to other structural sex deficiencies. On the other hand, the males of these same races are often defective in masculine qualities. They are not only more timorous and less aggressive than the males of higher races, but are not so masculine in their build and carriage, and men and women are more nearly of the same height. One obvious, if minor, result of this imperfect differentiation of sex has been alluded to by many travellers, and that is the difficulty of distinguishing at a little distance between the men and women when dress, proximity, or other circumstance has not provided a clue.

If we now turn to the women of civilised nations we see a being in whom the maternal functions have attained a very high degree of perfection. So marked is this in the case of some women as to give rise almost to malformation. The pelvis of such a woman is so wide that it interferes with active exercise, and similarly though to a less degree with the rounded contours and greater fatness of the female figure. The width of hip necessitates that the thighs should join the knees at a perceptible angle, suggestive of knock-knees, rendering her liable to outward dislocation of the patella, and giving an ungainly, waddling appearance when she runs. So long as she keeps to the more sedentary forms of exercise there is nothing

ungraceful in her appearance or bearing, for everyone sees that her configuration is eminently fitting to the purposes of her sex. But so soon as the womanly woman forsakes the more feminine forms of exertion, and attempts to indulge in hockey or cricket, it is noticed that she is awkward and ungraceful, and that her feminine "points" may even constitute positive disabilities. She is evidently putting herself to uses for which she is architecturally unfit.

On the other hand, we must all acknowledge an increasing tendency for the unmarried female to assume functions at one time considered to be the prerogatives of the male. This invasion of men's work and play is obviously the result of the preponderance of women in number, the raising of the age of marriage, the increase of luxury, and the decline of fertility. To all intents and purposes these serious changes render a larger and larger number of women virtually sexless, in so far as the production of offspring is concerned. In the process of natural adjustment to altered conditions the sexes almost necessarily rearrange themselves, so that, if the new circumstances continue, a time must come—if not already here—when there will be a division into male, female, and latent female, or neuter. This is foreshadowed in such books as Gissing's "*The Odd Women*," where the happiness and dignity of the working woman celibate is pointed out, and contrasted with the unhappiness of the unsuitably married. But, if this be true, it is inevitable that corresponding changes should take place in feminine structure, so that eventually a class may grow up fitted to cope with the more active, self-reliant life of the neuter. The militant female politician, strenuous hockey player, or so-called "advanced" feminine worker, in any walk of life, cannot continue to be handicapped by sex disabilities, and the increasing pressure and absorption of work must necessarily tend to lessen the importance of sex. More and more women throw themselves into such work, first as an alternative, and then in preference to marriage. Adaptation is a very speedy process, and already we see that this class of women can be distinguished from others by their attitude, carriage, behaviour. Alterations are taking place which go on lines divergent from those of sex, and apparently must end in virtual neutrality.

This third or neutral state arises from the absence of the katabolic element from the female circle, the presence of that element tending to increase her normal femininity.

The trend of modern life is therefore—so far as women are concerned—divergent. It influences the development of sex in the direction of excess on the one hand, and defect on the other. One

well-defined and special class of excessive development of sex must needs receive attention before we can pass on to a consideration of these defects and excesses in the adult. It must be obvious that sexual life may not only err by being too vigorous, but by continuing too long after it generally ceases; or, on the other hand, it may begin far too soon. In *sexual protraction* menstruation may continue for years after the ordinary time of the menopause. Drs. Gould and Pyle* quote many examples, including some well-authenticated instances of the continuance or reappearance of menstruation beyond the age of seventy, eighty, or even one hundred years. The catamenia in these cases is as a rule more than a mere flux, for it is sometimes interrupted by pregnancy, and cases have been recorded of the birth of children by mothers of between sixty and seventy.

Of far more importance from all points of view is *sexual precocity*, a form of over-development of sex occurring at a time of life when the reproductive organs are ordinarily in their bud stage.

Putting sexual protraction on one side as hardly of pathological importance, the subject of overgrowth or over-development of sex must be regarded as of two kinds, the one being sexual precocity and the other adult sexual overgrowth.

* 'Anomalies and Curiosities of Medicine,' p. 32.

II

OVERGROWTH AND PREMATURE DEVELOPMENT OF SEX

I. Sexual Precocity.*

WE have already seen that both cells and organs are liable to mature before their proper time, and that the same may be said of the man as a whole. Moreover, this prematurity may be either of progressive or of regressive development. If of regressive development then the changes which we associate with old age and decrepitude put a stop to existence long before it has reached its normal limits. But there is another kind of prematurity which brings the cell, or organ, or whole body, to its highest pitch of perfection at an abnormally early age, and yet, as a rule, has little, if any, accelerating effect upon declining development. This is the form of prematurity with which we are now concerned. It is sometimes termed "hypertrophy" (*i. e.* hyperplasia), and with perfect correctness, inasmuch as, for the time being, there may be undoubted overgrowth of tissue with corresponding functional excess. But it is often an overgrowth of temporary duration only, for as soon as other structures have had time to catch up the too hasty member the abnormality ceases. At other times the precocity does not fall into line with the immediate surroundings. The disproportion continues and ends in adult overgrowth.

Good examples of precocity of this nature are furnished by such "infant phenomena" as the calculating boys, boy preachers, artists, musicians, who flourish for a few years and are then no longer heard of. But now and then the ability remains extraordinary throughout

* Most of the facts mentioned here were taken from the admirable and exhaustive article by Mr. Roger Williams (with an abstract of over one hundred cases), published in the 'British Gynaecological Journal' of 1902, vol. xviii, p. 85. We are also especially indebted to Dr. V. Gautier's in the 'Rev. Méd. de la Suisse Romande,' 1884, t. iv, pp. 501, 553, 633, and to Drs. Gould and Pyle in their encyclopædic work on the 'Anomalies and Curiosities of Medicine.' Dr. Ploss, in his book, 'Das Weib,' furnishes some cases of sex precocity (Bd. i, S. 237), and deals with the whole subject of feminine development, anthropological and physiological.

life and the infant prodigy is known as a Macaulay, a Mozart, a Händel, a Spinoza, a Tasso, or a Kant.

So also with other organs than the mind. All are liable to assume an undue precocious importance, which may cease when the normal levelling up of early adult life comes to pass, or may continue for a time longer as adult overgrowth. Pre-pubic Graves's disease, obesity, gigantism, are all examples of precocity; but perhaps the best known of all is sexual precocity.

Though we shall here regard as sexual precocity all cases in which the organs of sex are obviously so far forward in their development as to constitute an abnormality, yet we can hardly with an open mind read the accounts of some cases of sexual precocity without wondering whether they were really of that nature in the first place. In some of them, for example, the skeletal or cutaneous or muscular precocity is so pronounced and arises at such an early stage as to suggest that in reality it came first, and that the sex precocity was merely an accompaniment. Thus, in Mr. Flint South's case* in a boy the most conspicuous characters at birth were his large size and generalised growth of black hair. It is true that the pudenda were noted to be larger than usual, so that at first he was thought to be ruptured, but it was not until he was four months old that the pubic hair and the sexual organs began to grow. His strength was remarkable throughout, so that when a year old, and 3 ft. 7 in. (109·2 cm.) high, he walked "extremely well," and at four and a half years could easily lift half a hundredweight (45 kg.) with one hand, and drag an adult along on his rocking horse. Again, in Moreau de la Sarthe's case† the boy weighed 16 lb. (7·25 kg.) at birth and was remarkably strong, but it was not until he was three that enlargement of the right testis was noticed, and it could not be said that he had attained puberty until he was six.

In many other cases it is remarked that the child was singularly big at birth, was precocious in teething, was hairy, or showed some other abnormality long before definite sex signs appeared.

Sexual Precocity a Variation.

Everything points to the conclusion that sexual precocity is a variation. Doubtless, in some cases the reproductive organs come to perfection too soon as the result partly of an inherent tendency, fostered, it may be, by an erotic or otherwise unwholesome, sex-

* 'Med.-Chir. Trans.,' vol. xii, 1812, p. 76.

† 'Journ. de Méd. Chir.,' etc., Paris, 1806, t. xii, p. 274.

stimulating environment. In other cases the precocity follows some serious illness. In such circumstances the variation is a minor variation.

But in most instances sensational enough to be thought worthy of publication the variation is major.

It is, however, a moot point as to whether we should regard the variation as progressive or regressive. Does it mark a step forward in the development of sex, or is it reminiscent of a by-gone time, when the sex functions came to maturity at an earlier age than they do now? There is reason to believe that it may be sometimes progressive at others regressive. Mr. Roger Williams makes a distinction between sexual precocity of earlier, and therefore more abnormal occurrence, and that which appears later. He says (p. 91), "Female precocity of the less extreme kind, such as that which supervenes between the normal period of puberty and the tenth year, is generally indicative of nutritive vigour and vitality in excess of the ordinary; thus precociously evolved females of this sort generally marry earlier, and have more children than the average. Emmet's statistics show this, for the eleven married females in his list—who commenced to menstruate at the tenth year, and whose average age at marriage was eighteen to twenty-five years—were impregnated fifty-nine times, which gives a higher average of fertility than was met with in those who commenced to menstruate at any other age." Evidently, precocity presenting these characters is a progressive condition, but in the extreme cases it is almost as certainly regressive. It is to these in particular that Delaunay's dictum,* "precocity is a sign of biological infirmity," applies. In order to appreciate this point we must first realise that, under normal conditions, the possession of distinctive sex instincts precedes puberty by many years. Boys and girls of four to eight years of age often show unmistakable sex preferences, and in some cases their talk and behaviour may be very decidedly lewd. Moreover, it is well known that in some sections of society the language of children of a somewhat older age, say from eight to ten years onwards, is habitually dissolute. Words of Saxon origin, monosyllabic, and applied only to the most primitive acts, are the current stock of everyday use, and no wit is so keenly relished as that which is founded upon the relations of the sexes. Neither must it be supposed that this necessarily indicates a base nature and inherent moral depravity, for many of the children who delight in this unchaste talk and behaviour will, in course of time, become model husbands and

* Quoted by Mr. Roger Williams.

fathers. Moreover, they will in after life wonder wherein lay the satisfaction which they experienced as children in indulging in such obscenity.

The explanation for this state of affairs is, of course, that the child, in recapitulating the stages of his ancestry, passes through a phase which corresponds with savage and semi-civilised eras of his evolution. But it is common experience of travellers that among the uncivilised of the present day matters are dealt with in the course of common conversation which appear to us unspeakably coarse and salacious. Hence, we conclude that children talk on these same subjects, and find a piquancy in immodest stories, for the same reason that they find satisfaction in climbing trees, in making caves and bonfires. They are merely repeating the ways and customs of their forefathers of a corresponding stage of evolution. At the same time there can be no doubt that conspicuous indecency in a child breaking out in spite of judicious training is indicative of a perilous state of mind or morals. It becomes morbid by sheer excess, and is a form of sexual precocity which may persist through life, marring the whole future existence. It is remarkable that though children are endowed with all the primitive instincts of sex, the consummation of those instincts is denied them. It is not easy to understand in what way this deprivation has been brought about, unless we regard it as sufficient explanation that it is of the utmost importance to our welfare, both as individuals and as a race, that the sex organs should not ripen and productive growth begin until the requirements of somatic growth have been satisfied, and we have acquired the faculty of controlling our desires.

At the same time this view of the subject will serve to show how sexual precocity may come, not as a progression, but as a reversion. It is a harking back to days when man was emerging from his simian existence. Probably it is for the same reason that sexual precocity is so often associated with pigmentation, or with hairiness; for extreme and universal hirsuties is frequently mentioned as a precedent or accompaniment of this condition. Perhaps of the same significance is the extraordinary muscular development which sometimes goes with sex precocity, and which causes some of the boys to resemble the infant Hercules. Nearly always this muscular overgrowth is a male characteristic, but occasionally it is noticed in females too, as in Dr. Rabb's case, presently to be mentioned. Apart from this explanation it seems strange that in some cases of pronounced sexual and general precocity the proportions of the body remain infantile or childish instead of assuming the adult form.

For example, in Dr. Howard's,* case a boy of three and a half years of age and 3 ft. 10 in. in height is represented in his photograph with the proportions of a seven year-old child. His head is big, and limbs short; the tibiae are strongly curved, and the middle point (in the photograph) is near the umbilicus. At the same time he is a sturdy-looking fellow, and seems to have well-grown muscles,



FIG. 15.—*Sexual precocity*: Aged $3\frac{1}{2}$ years. His height is that usual to boys of seven, but his sexual and muscular development are equal to those normal at seventeen. Yet the facial and bodily proportions are not in advance of his age. Compare with the picture of racial infantilism on p. 554. (From the 'New York Medical Journal,' 1892, p. 661.)

especially of the lower limbs, reminding one of sexual ateleiosis, or of an African pygmy.

Another associated developmental condition pointing to the same conclusion is the frequently mentioned defective intelligence. This is by no means always present, and cannot therefore be regarded as a necessary part of the disorder, and neither can it, for the same

* 'New York Med. Journ.,' 1892, p. 661.

reason, be lightly brushed on one side as a consequence of the sexual precocity. It seems more likely that it is a correlated condition, and



FIG. 16.—*Dr. Abram's case of sexual precocity*: Aged 8 years. The characters are hermaphrodite, the special organs of sex being feminine, but the contours of the body and face masculine. The chest and shoulders are broad, the pelvis narrow, the muscles prominent; there are no breasts. Note the rickety enlargement of the wrists and ankles. The limbs are short in comparison with the trunk, and the head big, as in normal childhood.

reminiscent of a period of evolution when the brain faculties were of a very low order.

A peculiarity which must be regarded as atavistic in nature is the

occasional occurrence of opposite sex characters. This is, in all probability, a reversion to a state when sex was far less well defined than it is now, such as will presently be referred to under the heading of post-natal hermaphrodism. An excellent example of this partial hermaphrodism is that recorded by Dr. Rabb,* in which a girl, aged 4 years, menstruating regularly and with fully developed breasts, possessed a coarse, masculine voice, and muscular strength equal to that of a fully-grown man. Her skin also, except on the face and the palms of her hands and soles of her feet, was entirely hidden under a dense crop of soft and downy hair. In other cases children with feminine sex organs grow masculine facial hair, as in Matthew Baillie's† case, in which there was a strong voice, and the appearance of an incipient beard, whiskers, and moustache; and though the internal organs of sex were feminine, the clitoris was one inch in length.

But perhaps the most remarkable example of masculinism of this kind is an unpublished case of Dr. Abram's, which has already received attention as a case of pernicious anæmia on p. 403. In this patient the sex characters were so mixed that, in default of a *post-mortem* examination, it seems quite impossible to say whether there was more of the feminine or more of the masculine in "her" composition.

Other Associated Abnormalities.

One of the most interesting of the accompaniments of the premature development of sex are *rickets* and *chlorosis*. Both of these disorders we regard as overgrowths, as we have explained in the third part of this book. Hence we are by no means surprised when we find that overgrowth of sex organs is correlated with similar overgrowth of the blood or of the bones. We have seen how the special characters of skeletal overgrowth in rickets is calculated to frustrate the legitimate efforts of developing bone, and are therefore prepared to be told by Mr. Roger Williams that a large number of precocious children suffer from rickets, and that where this is the case their dentition and skeletal growth are decidedly impaired, whereas where there is no associated rickets dentition and skeletal growths are also precocious.

The bearings of this point have already been alluded to in the chapter dealing with rickets (see p. 423).

* 'Nashville Journ. of Med. and Surg.,' January, 1878 ('Brit. Med. Journ.,' "Epitome").

† 'Med.-Chir. Trans.,' vol. xi, 1811, p. 17.

The overgrowth of the blood, which we term "chlorosis," is also a fitting accompaniment of sexual overgrowth (see p. 372).

Obesity is another concomitant which is probably of the same category. It occurs pretty often, and is sometimes associated with *hirsuties*. Dr. Guthrie,* in reporting an interesting case of his own, has alluded to other cases of combined obesity and sex precocity (see p. 509). In Dr. Rabb's case the secretion of sweat was extraordinarily increased, so that in a quarter of an hour after being washed and dressed the clothes would be saturated with sweat of highly offensive odour and of a dark yellow colour.

In one case (Hahn's) there was "hypertrophy" of both hands; in another (Jacobson's) there was *giant growth* of the genitals, face, left side of trunk, and all the limbs. In Dodd's case there were only three toes on the left foot. *Hydrocephalus* is mentioned in four cases. Dr. Abram's case (see p. 403) of sexual precocity associated with evidences of *pernicious anæmia* must also be mentioned here.

One of the most interesting associations is *tumour formation*. Mr. Roger Williams found that of thirteen cases of female sexual precocity coincident with intra-abdominal tumours, eleven were of ovarian and two of adrenal origin, ten being sarcomata, two cystomata, and one fibroma, and at least six more cases are recorded by other writers.

Perhaps the most important article on this subject is that by Drs. Bulloch and Sequeira,† who have collected twelve cases of sex precocity associated with supra-renal cancer. They found, moreover, four cases of "hypertrophy" of the supra-renals co-existing with hermaphroditism, genital hypertrophy, or somatic overgrowth, and three of atrophy with sex deficiency. But that the relation is not causal seems to be proved by the occurrence of sex precocity with tumours not of the supra-renal, but of the pineal, thymus, or pituitary body, or, more often, without tumour formation. Tumours may also occur in the supra-renals (14 cases) without undue sex development.

Two of the cases of precocious sex were in males and were correlated with *muscular overgrowth*.

Hereditv.

In some of the reports on cases of sexual precocity it is asserted that the reproductive instincts of the parents were unusually pronounced. Moreover, this is not always the result of mere fancy bred by the sight of the malformation. This, at any rate, cannot be

* 'Trans. Clin. Soc.,' 1906, vol. xxxix, p. 252.

† 'Trans. Path. Soc.,' vol. lvi, 1905, p. 189.

said of Dr. Plumb's case,* in which, before the birth of the child, the husband dwelt upon the "very strong generative instincts" with which both his wife and himself had been endowed by Nature. When this child came into the world the very natural inference was drawn that there was some hereditary connection between the sexual proclivities of the parents and the facts that the external genitals of the baby were in form and development like those of a woman of fifteen, and that at the age of six weeks menstruation appeared and continued at intervals of six weeks.

In other cases the brothers and sisters are sexually precocious, as in Lesser's† case, in which menstruation beginning in a child of three was followed at four by hirsuties, which covered the body, and especially the lower limbs, with an abundant crop of hair, and appeared as whiskers on the face. The intelligence was advanced, and two brothers, one of sixteen and the other of twelve years, had precocious beards. In this case it is, of course, possible that the heredity was of the hairiness and not of the sexual precocity.

In Stone's case‡ it was stated by the father that he had himself been sexually premature and had had sexual indulgence at eight.

One result of this tendency to transmission is the occurrence of precocious grandparents, so that we read§ of grandparents of twenty-nine, of twenty-eight, of twenty-five, and even of twenty-one, though this last case can hardly be regarded as authentic.

Varieties.

Sexual prematurity varies widely in its manifestations, from a mere overgrowth of some satellite organ, such as of the larynx or of one breast, to a generalised overgrowth of the whole reproductive apparatus, every organ being implicated in its proper proportion. V. Gautier has proposed a classification based upon these variations, but Roger Williams regards the divisions as artificial.

Course and event.—Premature sex development of pronounced degree, constituting a regressive variation, eventually results in a stunting of the body, much as we might expect of a reversionary process. Moreover, there is reason to believe that the menopause sets in long before its usual time, so that the duration of sexual life is not lengthened, but cut short. Further, in many cases the

* 'New York Med. Journ.,' 1897, vol. lxxv, p. 768.

† 'Revue des Sci. Méd.,' 1897, tome I, p. 213.

‡ 'Amer. Journ. Med. Sci.,' vol. xxiv, 1852, p. 561.

§ Drs. Gould and Pyle, 'Anomalies and Curiosities of Medicine,' p. 38.

somatic life is also curtailed. To these the words of Bacon* are applicable when he wrote—"There be some have an over-early ripeness in their years, which fadeth betimes."

Sometimes the cause of death is said to be "debility," the result of the exhausting demands of menstruation or of the male organs upon the vitality of young children. A case which seems to have ended in this way is recorded by Pliny in his 'Natural History,' when he writes that in Salamis, Euthimides had a son who grew to three Roman cubits (141 cm.) in three years; he was said to have little wit, a dull mind, and a slow and heavy gait; his voice was manly, and he died at three of general debility.†

In another case, described by Clifford Allbutt,‡ a child menstruated at the eighteenth, nineteenth, twentieth, and twenty-second months, each time falling into a hectic, and at the last died "wasted and exhausted," though there were no other signs of puberty. Probably of the same nature is a case quoted in Davis's 'Obstetric Medicine,'§ in which a girl of four, "became a menstruous subject," and her features "exhibited characters of a corresponding senescence," and in her eighth year she became the subject of constitutional debility and died, though she presented no other evidence of disease. But occasionally definite signs of senile degeneration, such as greyness of hair, baldness, atheroma, appear, heralding the onset of premature old age. Some cases of this kind will be presently referred to under the head of "senilism."

The following case is, perhaps, worth recording, if only for the reason that we have had her under observation from the ages of two to eighteen years, when she had settled down into a short, perhaps a little dull-witted, but otherwise normal, individual:

She was illegitimate, began to menstruate at the age of thirteen months, and continued to do so at irregular intervals until she was eight, when she became more regular. After the onset of menstruation she started to grow rapidly, until, at the age of three and a half years, when the photograph was taken, she had attained a height of 146 cm., a weight of 41·580 kg., a skeletal development, as shown by X rays, equal to that of most girls of eight, and the sexual development usually met with at thirteen or fourteen. At the same time the sense of modesty was fairly conspicuous, and with it was manifested a perceptible coyness. Her intelligence was backward,

* Essay, 'Of Youth and Age.'

† From Gould and Pyle's 'Anomalies and Curiosities of Medicine,' p. 343.

‡ 'Med-Chir. Trans.,' 1866, p. 161.

§ Vol. i, 1836, p. 237. From 'Ephemerid Germanic,' dec. 3, An. 7, 8.

so that she could not get beyond the third standard at school. During some five or six years she made her appearance at intervals



FIG. 17.—*Sexual precocity*: Girl, aged $3\frac{1}{2}$ years, with sexual development usual at twelve or thirteen, though the limbs, and especially the upper limbs, are still of childish shortness.

to be treated for recurring chlorosis, but at the age of twelve, or thereabout, she became permanently well in this respect. She attained her full height of 151 cm. at six, and is now, therefore, 7 cm. under the average female height.

II. Adult Sexual Overgrowth.

In this condition either masculine qualities are exaggerated to a morbid or semi-morbid degree, or feminine qualities are increased into an unnatural effeminacy. Either of these extremes is liable to arise where circumstances are favourable, and each is attended with its appropriate morbid consequence. Thus, when men are herded together for purposes of war, or for the pioneer work requisite in the opening up of new territory, the artificial state of society which is implied leads in time to the appearance of symptoms quite as disastrous, and therefore quite as unnatural, as are those brought about by any other physiological deprivation or excess. Those virtues of self-reliance, courage, indifference to physical discomfort, which we associate with manhood, are then apt to degenerate into recklessness, ferocity, or brutality, leading the individual into all sorts of unnecessary dangers, and cutting short his life just as effectually as if he were the subject of infantilism or senilism, or had become vulnerable to the attacks of micro-organisms.

So also among women an exclusively feminine and idle society is prone to produce its crops of neurotics, and of the mentally and physically feeble, to a far higher degree than when females are judiciously intermingled among males. The virtues associated with the feminine character are, under such circumstances, prone to deteriorate into vices, and the exaggerated, morbid femininity which results has effects which are equivalent to those of a disease.

III

UNDERGROWTH AND UNDER-DEVELOPMENT OF SEX

If the unbalanced development of masculine or feminine qualities tend to results tantamount to those of disease, still more is this true of lack of development of these qualities. Sexual indifference leads either to sterility, or to the propagation of small and infertile families. It is one of the chief causes of the decay and extinction of well-known and gifted names, and is therefore of as much importance, from a biological point of view, as hereditary syphilis, or any other sterilising disease.

Little, however, need now be said upon this subject, because whatever is true of under-sexuality, in this respect, applies also to hermaphrodisism, with which this affection is closely allied.

IV

MASCULINISM AND FEMINISM, OR POST-NATAL HERMAPHRODISM

THE word "hermaphrodisism" is usually applied where characters distinctive of one sex are found at birth mixed with those distinctive of the other sex.

But, in reality, this condition does not originate solely in pre-natal days, for contrary sex qualities sometimes do not appear until adult life. Moreover, these morbid alterations are then not solely changes of function, but correspond with structural changes. These structural changes, it is true, are not nearly so pronounced as in hermaphrodisism of pre-natal origin, but are nevertheless undoubtedly to be detected.

I. Feminism.

Feminism in the male must be distinguished from infantilism. The condition is characterised, not so much by the passive absence of male qualities, as by the presence of those of positive female type. Thus it is not sufficient that the sexual organs are undeveloped. This may be only a temporary affair, as in a case recorded by Curling* in which a man, aged 26 years, was possessed of the sexual organs of a boy of eight. Yet he married and had children, and at the age of twenty-eight the sexual organs were of normal development.

Moreover, "ill-development of the testes, even to the point of complete sexual incompetence," may be associated with all the external bodily characters of the male.†

But complete absence of the primary male organs of generation is probably always associated with feminism. Removal of the testes in young boys results in the acquirement of characters which are intermediate between those of men and women, but approach rather to the latter than the former. "The eunuch is usually large, fat, and flabby, with scanty hair on the face. His pelvis is broader and his shoulders are narrower than those of the entire man; his features

* Taylor's 'Medical Jurisprudence,' p. 868.

† Dr Griffiths, 'Clinical Sketches,' June, 1895.

simulate those of the female, and his voice remains like that of a boy.”*

In complete non-development of the sexual organs, or in cases of their removal in early childhood, the result, as a rule, is that “the stature is dwarfed, the cellular tissue accumulates fat, the breasts become full, the voice at puberty fails to break and retains the feminine pitch, and the beard remains undeveloped.”†

Feminism may be the result of changes which set in before the usual onset of puberty or after the cessation of sexual life.

It is, therefore, dependent upon non-development of the sexual organs on the one hand, or upon too great a swing of the pendulum on the other. In other words, it results either from imperfect development or from premature degeneration.

Feminism, the result of degenerative sexual changes carried to excess, shows itself in the form of a timid, hesitating manner, indecision of character, an effeminate appearance, and, in its extreme form, a decided partiality for the same sex.

Such men are sometimes obliquely referred to under the more or less true, if contemptuous, epithet of “old women,” or “old women of the opposite sex.”

Feminism varies widely in degree, from the mere possession of general feminine characters, without structural changes, to a complete perversion of all save the essential organs of sex. Thus one breast may alone be affected, constituting unilateral gynæcomastia, or both may be enlarged, with or without enlargement of the nipples. In some cases the glands secrete milk, so that instances have been reported of the father of a family taking upon himself to suckle his own baby, or of the father sharing that function with the mother.‡

As a rule, in the enlarged breasts of the male the increase in size is of the nature of degenerative hyperplasia, that is to say, there is gland-tissue present, but it is not functional, and is mixed with large quantities of connective tissue.§ Nevertheless, appearances may occasionally be found under the microscope which seem to show that a true functional overgrowth sometimes precedes the degenerative hyperplasia. This was the case, for example, in a specimen exhibited by Mr. Jones and Dr. Christophersen,|| and

* *Ibid.*

† ‘Guy’s Hospital Gazette,’ 1898, p. 524.

‡ Gould and Pyle, ‘Anomalies and Curiosities of Medicine,’ p. 397.

§ Stieda, ‘Beiträge z. klin. Chirurg.,’ 1895, Bd. xiv, Heft 1, S. 179.

|| ‘Lancet,’ 1904, vol. i, p. 865.

histologically examined by Mr. Shattock. Mr. Shattock reported that "the increase in size is due to dense (though well-developed) fibrous tissue. But it should be classed as hypertrophy, and not elephantiasis or fibrosis, since the number of acini is not less than in the normal female breast. The epithelium is proliferating, but there is only here and there evidence of interstitial inflammation. One must regard the breast as hypertrophied, and, in addition, the seat of a parenchymatous mastitis."

Feminism as a Continuous Variation.

This form of hermaphroditism occurs whenever an inborn tendency for the male to assume female characteristics is not strong enough to produce effects unless aided by a suitable environment. Such cases are not uncommon. It is evidenced by obesity, premature failure of virility, and a timid disposition. It also occurs in people of unsound mind, or loose moral control, and probably accounts for most cases of criminal attachment of men of middle or old age to those of the same sex.

A case in point is apparently furnished by a well-known public character, who lived during the latter half of the last century. A man of exceptional brilliance of intellect, of the type commonly termed "clever," he early in his career gave his mind to the subject of personal adornment, his dress designs for women being always of the languishing, and those for men of the effeminate order. Meanwhile his own habit of body, dress, attitudes, and ideas showed distinct leanings towards the feminine. He became fat, his face assumed a markedly female roundness of outline, which was heightened by the length and waviness of his hair. As the leader of a cult, the worship of his disciples, chiefly women, tended greatly to fix and accentuate his peculiarities. Subsequently he showed such loose and sensual partiality for those of the same sex that he was arrested, tried, and imprisoned. Eventually abandoned by those who, by their over-adulation, were in part responsible for his downfall, he died miserably in Paris.

It is, of course, open to anyone to assert that the feminism depicted here was a major, not a minor, variation, and that he would have remained effeminate in whatever walk of life he had been placed. Such a view is supported by the fact that the feminism was associated with genius, for he was a poet, playwright, and wit of singular ability.

Feminism as a Discontinuous Variation.

Feminism is often *associated* with some other developmental disorder, either in the same individual or in his family. In the latter it, of course, constitutes a form of heredity (transforming heredity). Thus Mr. Hutchinson, in his 'Archives,' describes an instance of feminism in a boy of fifteen whose mother was the subject of *acromegaly*. In this case there was extreme hypoplasia of the generative organs, a development of the breast and nipple causing them to be equal to those of a well-grown woman, as well as general obesity. As frequently happens, in this case there was not only feminism, but some delay of general development, constituting infantilism.

In 'Caulfield's Wonderful Characters' a man is figured with the breasts of a female, and with a *pre-natal defect of development* of the right upper extremity, so that a miniature finger projects from the shoulder.

Feminism of this pronounced degree occurs independently of surroundings, and is a true discontinuous variation. It is often hereditary, the heredity, of course, being of the family kind.

One of the most common and important of the conditions associated with feminism is *obesity*. This obesity is, indeed, so frequently a concomitant of feminism that the fact is taken advantage of commercially in the artificial fattening of meat-yielding animals by the method of spaying. In this case the obesity is consecutive to the deprivation of sex.

But that this is not necessarily the relation between the two is suggested by the fact that the obesity sometimes begins long before the time has arrived for the perfection of the sexual organs. The obesity may, indeed, show itself before birth, as in a case which once came under our observation.

The first notice of this case was in a letter to the 'Lancet'* by Mr. Yorke Davies. He says: "A thin little woman gave birth to a male child sixteen months ago. When born the child was of ordinary size in every way. It now weighs and measures as follows: 36 in. (91 cm.) long; round the abdomen, 33 in. (83 cm.); chest, 30 in. (76 cm.); thigh, 17 in. (43 cm.); calf, 11½ in. (38 cm.). It is perfectly impossible for anyone to conceive its extraordinary appearance without seeing it. Its weight is 4 st. 8 lb. (29 kg.). The father is a man of ordinary stature. The infant seems very happy and

* 'Lancet,' 1886, vol. ii, p. 30.

intelligent, but on account of its enormous weight it cannot be lifted without expressing pain."



FIG. 18.—*Feminism*: Defective development of sex, combined with opposite sex characters (obesity, gynæcomastia), in a boy, aged 11½ years.

In after life this case developed into one of feminism, as will appear in the portrait.

In September, 1896, when he was eleven and a half years old, his height was 147·5 cm. and weight 74·84 kilos. The middle point of total height was at the symphysis pubis. His sexual organs were conspicuously under-developed, but the breasts were full, though there was no true breast substance. He did not lack intelligence, and was strong, and capable of walking many miles without fatigue.

Racial Feminism.

As may be expected, feminism is more often met with among semi-civilised and savage races than among those which are civilised. Sir Harry Johnston* and Dr. Crispini† say that gynæcomastia is not uncommon among the Sndanese. Sir Jonathan Hutchinson‡ found it to be much more frequent among Hindoos than among Europeans. He attributes it to their conditions of life. "Wherever the members of the two sexes follow the same occupations, and live upon the same food (as regards both quantity and quality), then the distinctive features of sex will tend to diminish." The Hindoo environment is of such a nature as to react upon their sexual characters. They are an effeminate race, and their effeminacy often crosses the borderland of defective differentiation of sex, to become positive feminism. The inhabitants of Southern China and of Burma may also be regarded as in a state of racial feminism.

Acromegalic Feminism: Feminism with Gigantism.

One of the features of acromegaly is defective development of the sexual organs. This, in some cases, appears to lead to actual feminism. Instances are recorded of the combination of feminism with gigantism. It is highly probable that these are in reality acromegalic, though there seems no reason why mere overgrowth of the skeleton should not be associated with feminism. In Dr. Hallopeau's§ case of gigantism with feminism, the man was thirty-eight years of age and 1·85 m. high. Facial hair was absent, except for a slight growth on the upper lip. The breasts and pelvis were well developed, and the sexual organs were like those of a small child. In some cases of gigantism feminism is so intermingled with infantilism that it is not easy to say which preponderates.

* 'British Central Africa,' p. 399.

† 'Lancet,' 1904, vol. i, p. 1499.

‡ 'The Polyclinic,' 1905, p. 258.

§ 'La Semaine Médicale,' vol. xix, 1899, p. 53.

II. Masculinism.

According to Dr. McCann,* masculinity of women should be divided into two groups.

In the one the primary generative organs are well formed, so that there is no impediment to conception and child-birth.

In the other the primary generative organs are abnormal.

All degrees of variation are met with. Among those of the first group—with perfect generative organs—the breasts, the configuration of the body, the voice, or even the physiognomy, or the manner, may alone be masculine, the individual being in all other respects well developed. Sometimes there is a condition which corresponds inversely with the gynæcomastia of males. In that event the breasts are undeveloped, the voice is masculine, and there is a tendency to the growth of hair on the face and to the development of a coarser type of feature than is usual among females. In extreme cases the breasts are of the male pattern, the voice is masculine, and so also is the pelvis. Indeed, so completely may the secondary sexual characters be transposed that male clothing may be adopted without fear of discovery of the sex of the woman. In such cases there may be a corresponding weakness or perversion of the sexual instincts, and there is good reason to believe that some well-known cases of the adoption of male dress and male habits by women have been no more than the expression of a masculine tendency.

In the second group—that in which the primary sexual organs are undeveloped—there may be no other malformation, or one or more of the secondary characters may be in abeyance. All grades of defect are met with between complete masculinism and a trivial ill-development of some one detail of the generative structures.

It is possible for a secondary perversion to be very conspicuous, though the actual feminism is but slight, and *vice-versâ*. Thus the long beard, whiskers and moustache of a “bearded woman” may stand so completely alone that it seems almost a misnomer to use the term “masculinism” at all. Some such bearded women are in all other respects eminently feminine. The growth of hair may, indeed, be but part of a general hirsuties, and a dermal, rather than a sexual, deformity. That such is the case is further indicated by the tendency for the hairiness to be associated with dental malformations while other sexual characters remain unaffected, showing pretty conclusively that the condition is a disorder of the appendages of the skin rather than of the appendages of the genital apparatus.

* ‘Amer. Journ. Med. Sci.,’ vol. cxii, 1896, p. 392.

Many women acquire some faint masculine character after the cessation of sexual life, and now and then this masculinism is so pronounced as to become pathological. A definite beard or moustache appears, and the sexual instincts may even swing over into a partiality for those of the same sex. This peculiarity is especially observed in the subjects of pre-natal hermaphroditism. These may manifest female instincts during early maturity, but upon the cessation of the menses, which is apt to occur at a very early age, a state of masculinism supervenes, and under such circumstances the individual has been known to don male dress and pass as a man, though in reality a woman.*

As in feminism, so in masculinism, some are solely the result of discontinuous *variation*, and others are the result partly of continuous variation and partly of environment.

Racial Masculinism.

Among many savage races, where the females are subjected to conditions involving great hardship, the feminine qualities are in abeyance, so that the differentiation between men and women is not well marked. But if it be the custom of a race or people to put its women into positions of responsibility, making them assume the functions of men, definite masculine characters are prone to appear. This, for example, is what happened to the amazons of Dahome. Captain Burton and Mr. Duncan, who visited the country before it had come under the influence of modern trade, found that the usual social and political relations of the sexes were reversed. "Fierce, cruel, relentless, deprived by severe laws of all social ties, the women soldiers of Dahome are the only real fighters, the men soldiers being comparatively feeble and useless." "There is a powerful *esprit de corps* reigning among the amazons, who are fond of boasting that they are not women, but men. They certainly look as if they were, being, as a rule, more masculine in appearance than the male soldiers—tall, muscular, and possessed of unflinching courage and ruthless cruelty."†

* Gould and Pyle, 'Anomalies and Curiosities of Medicine,' p. 208.

† The Rev. J. G. Wood, 'The Natural History of Man,' vol. i, pp. 636-8.

SECTION IV

Centenarianism *

Longevity is, as a rule, partly the result of adaptation to a suitable environment; partly to minor variation. The normal limit of life is a little over three score years and ten. Deaths from senile causes occurring before this date may be attributed to regressive variation (senilism), after this date to progressive variation (centenarianism).

THE longevity of any individual depends on two factors—

(1) One of these is the care with which he orders his life. He may prolong his existence by means of favourable circumstances or environment, terms which include all those sanitary desiderata of good food, suitable clothing, abundance of fresh air and of clean water, a quiet, peaceful mode of life and pleasant society. Though he may by these means add a few years to his life, yet, to quote Dr. Rolleston: "However careful he may be—and though he may escape injuries, illness, and great mental and emotional strains—it is almost inconceivable that he will thereby attain the age of one hundred, or even come within ten years of one hundred."

(2) Of greater consequence than his manner of life in determining its duration is the longevity of his ancestors. If he come from a long-lived family his carefulness will ensure that he, too, will live long, perhaps a few more years than his predecessors have lived. But if the family history reveal a tendency to die from senile affections at an early age, he, too, must not expect to survive for more than a few years beyond the age which they attained. Hence to the moderately careful man inheritance is of more importance than environment in the duration of life.

Though it is impossible definitely to say at what age longevity ceases to be normal and becomes abnormal, yet for all practical purposes we cannot be far wrong if we regard every one who lives

* Though hardly a disease, excessive length of life is included here for the sake of completeness. It is a biological extreme, and therefore an abnormality, comparable with muscular overgrowth and with genius.

ten years longer than the normal age of death as exceptionally old, and any one who dies ten or more years earlier than that normal age as exceptionally short-lived.

Evidently the main consideration must be to find the normal duration of life. This, at first, seems impossible, but has apparently been accomplished by Professor Lexis.* He shows that the general male death-rate in Prussia manifestly rises round about the age of seventy (seventy-one among women), and then suddenly drops, so that if we make allowances in accordance with the mathematical theory of error, there is every indication that this is the normal limit of life. This normal limit varies between sixty-seven in the case of Belgian figures to seventy-four in Norwegian.

In our own country the ages are seventy-two for men and seventy-three for women.

Any individual who lives to eighty, and by so doing enters upon a stretch of life which is abnormal, becomes more abnormal the longer he lives, and must come within the definition of a *minor variation*. His exceptional age is the result of two factors, the one being an innate tendency to live long, fostered to some extent by the other, namely, a fitting environment.

But sometimes, as a rare event, the inherent faculty of persistence of life seems to assert itself independently of environment. The individual, like the Struldbrugs of Swift, is apparently set aside from birth for prolonged existence. His parents and grandparents may have lived lives of average duration. He himself may have suffered from many diseases and endured much hardship, or have even indulged in frequent bouts of alcoholic excess, and yet continues living, retaining the features of middle age into the time usually occupied by old age, and so thriving until he becomes a centenarian.

Sir Ray Lankester† holds that those who have lived into centenarianism should be regarded as on a par with giants. They are, in fact, progressive *major variations*.

This is indicated by (1) their rarity, (2) their occasional heredity, and (3) their occurrence despite unfavourable circumstances.

(1) Their *rarity* is such that the deaths in one year (1905) of those in England who have attained one hundred are less than one hundred, though the general mortality *per annum* is 670,000.

(2) Their *hereditary transmission* is, if we may judge from newspaper reports, not infrequent. In one, commented upon by the

* 'Zur Theorie der Massenerscheinungen,' 1877, pp. 42-64.

† 'The Advancement of Science,' 1890, p. 237.

'Lancet,'* the age of a man of 105, who had died in Blackburn Workhouse, had been verified by the master. This old man was a snuff-taker, habitual smoker, and "was not averse to a glass of beer," and it is stated that his mother had lived to 105, and a sister had been killed at 102.

In the daily papers of this year (1908), as we are writing this chapter, there are notices of three such cases of heredity, the most striking of which is as follows: "Mrs. Pamela Priday has just died at her home at Quedgeley, near Gloucester, aged 102. Her father lived to be over a hundred, her paternal grandparents were both centenarians, and her eldest brother was in his hundredth year when he died."

(3) *The continuance of life notwithstanding adverse conditions* is a marked feature of centenarianism.

Professor Humphry remarks of the fifty-two centenarians of his list that "many had been engaged in hard bodily toil or mental work." One, a man, declared, "I always drunk as much as I could, and always will do." A second and a third, poor women, had been subject to much exposure, and had had a rough life, following the Army in various parts of the world. "Most were temperate and small eaters, particularly of meat, but some partook rather freely of animal food; many slept well; in others sleep was said to be short, indifferent, or bad. Two were demented, and several had had severe illnesses," some up to the very end of their long lives, yet, continues Prof. Humphry, "it is not unsatisfactory to find that the effects of illnesses, even when severe, do not always preclude longevity." These illnesses included rheumatic fever, epilepsy, gall-stones, insanity, peritonitis; one had had fever, and on other occasions jaundice and smallpox; others had had renal disease, bronchitis, and paralysis. Many had recovered from disease when at great age.

Probably every doctor who has had a few years' experience in private practice can call to mind instances of the predominance of an inborn vitality over circumstances which strongly tend to cut life short. We ourselves became acquainted with a remarkable example a few months ago. In a well-to-do family the father came of a long-lived stock, and the mother was the daughter and granddaughter of forbears who died young. There were two sons, both of whom took after the father in appearance and character, and three daughters, all of whom resembled their mother. The mother died when between thirty and forty years of age from Graves's disease;

* 1904, vol. i, p. 1503.

two of the daughters died before the age of thirty, one from acute tuberculosis, another from Hodgkin's disease, and the third is still alive, and is about forty years of age. The mother and daughters were quiet-living, abstemious, and careful. On the other hand, the father and two sons were entirely different from the feminine part of the family, both in appearance and disposition. The father has attained the age of seventy, though he looks between fifty and sixty. For some twenty years his habits have been regular, for he has invariably consumed his bottle of whisky each day, besides half a bottle of port wine, and as the night approaches he is consistently in a state which cannot be termed sober, though he never loses self-control. He has always drunk to excess. His two sons are also in good health, although they are drunkards.

One of the "pot-boilers," translated by Goldsmith when he first came to London, was 'The Autobiography of a French Protestant,' who had been condemned to the galleys for attempting to escape from the country after the Revocation of the Edict of Nantes. This interesting book contains a vivid and heart-rending account of hardships endured with heroic fortitude under almost intolerable conditions. As one reads of the cruel overwork, of the coarse, monotonous, and inadequate food, of nights spent in attempts to ease the galling of chains, of the cold, and of the loathsome insanitation, it seems marvellous that he should have lived even for a year. Yet, that his account of these hardships is in no wise exaggerated, can be proved from the memoirs of Vidocq, who was for a few years a galley-slave himself. In spite of his atrocious treatment, the Protestant not only endured this slavery for more than twelve years (from 1700 to 1713), but afterwards lived a busy, useful life, and did not die until 1777, or sixty-four years afterwards, at the age of ninety-three.

We have seen only one centenarian.

This is a lady who died at nearly one hundred and three. We saw her with Dr. Ivon Hawes, of Whitechurch, when she had passed her one hundred and first birthday. She was then suffering from influenza and was very ill, taking hardly any food, conscious only when roused, and lapsing immediately afterwards into muttering delirium. Her pulse was 110 per minute, soft, dicrotic, and intermittent. Judging her prospects from experience of the illnesses of other people, we prophesied that she would die within a few days, Dr. Ivon Hawes demurred from this view, for he had before attended her for two separate attacks of influenza, and had each time seen her in a similar condition. On the first occasion he had felt certain that the illness would be fatal, yet she had recovered, and he had no doubt that she would now

recover from this third attack. Despite his opinion, founded upon such experience, it seemed almost incredible that recovery should take place; yet the event proved that Dr. Hawes was right, for she gradually rallied, and again became able to take an interest in life, though she never recovered her old spirits and activity.

In the last year of her life her eyes were bright, showing not a trace of *arcus senilis*, and her face had again become plump, so that many old wrinkles were smoothed out. Moreover, the skin of her hands was remarkably young-looking, no tendons nor veins being visible. It was smooth and soft, and so different from the dry, wrinkled, harsh, loose skin of old age, that one would judge her hands to be those of a lady of fifty. After her last illness she gradually became helpless and bedridden, finally dying when within six weeks of her one hundred and fourth birthday.

It may be added that the life led by this old lady during her prime had not been one of ease and peaceful idleness, such as is supposed to account for the long lives of many old maids, but had been one of activity, bringing her eventually into a wide circle of friends.

No case can better illustrate the essentially abnormal condition which is implied in centenarianism. We must all recognise that nothing can be more deadly to ordinary old folk of from seventy-five to eighty than influenza, even of mild degree, and the very fact that a lady of one hundred or thereabouts should survive three attacks of influenza, in one of which she became delirious, almost unconscious, and apparently moribund, is in itself evidence that centenarianism must be put into a class essentially distinct from that of ordinary old age.

The influenza must be regarded as an environment of a peculiarly unfavourable kind, and her survival as evidence of the presence of a strongly inherent vitality.

Everything points to the conclusion that centenarianism is a progressive variation of major degree, and, like all such discontinuous variations, crops up spontaneously apart from circumstances. If this be correct it is obvious that the habits of centenarians are of no value as a guide to the attainment of long life. Furthermore, if it be to the benefit of mankind that life should be prolonged to its utmost limit, the best way of securing that end is to encourage the intermarriage of the grandchildren of centenarians. If eugenics can bring about such artificial and deliberate selection it is conceivable that we may not only gain the advantage of a prolongation of life, but also a longer period of useful and happy existence, increased resistance to microbial disease, and, in short, all that is implied in a hardier and more vigorous stock.

SECTION V

Morbid Delay of Progressive Development or Infantilism

I

INTRODUCTION

Infantilism is either evolutionary or developmental. Developmental infantilism occurs either as a minor or a major variation. There are also two types, Brissaud's, or the myxœdematous, and Lorain's, or the anangioplasic.

Causes and Classification of Infantilism.

We have seen that evolutionary infantilism is the product of many depressing conditions. It is the life in the desert, in gloomy forests, or among mountains that tends to retard the development of the Akkas, Obongos, or Bosjesmans. But let depressing conditions of life be brought to bear upon certain sections of people of normal development and again infantilism results. This is well shown in our big cities. Some of the dwellers in the East End of London are subjected to hardships akin to those suffered by people affected with evolutionary infantilism. They live from hand to mouth, do not get sufficient food, spend their days in sordid courts and their nights in overcrowded airless dwellings, with the result that they are affected with what is almost tantamount to endemic infantilism. They are of poor physique, and are warped, both in body and mind, live short lives, readily succumb to disease, and break down with senile decay at an unusually early age. There is a marked difference in these respects between the dwellers in the east of London and in the west. Nothing shows this better than the tables included in the article, "Hygiene of Youth," written by Dr. Clement Dukes for Allbutt and Rolleston's 'System of Medicine' (vol. i, p. 162,

2nd ed.). These show very graphically that the weight and height of boys and young men of the educated classes markedly exceed the weight and height of the town-bred population of the poorer classes of similar ages.

Further, it is exactly this same kind of causes which accounts for sporadic infantilism of minor or fluctuational type. In all cases the important factor is the environment. Let the conditions of life be depressing in character and the development will suffer, no matter whether those affected be races, large sections of people, or individuals.

Nothing, perhaps, contributes more largely to the inferiority in physique of slum dwellers than alcohol. In the East End of London the most miserable and degraded specimens of humanity are to be found hanging about the doors of public-houses. It would be difficult to say which produces the greater deterioration, alcohol or syphilis, though there can be no doubt that the combination of the two is worst of all. Alcohol always has most effect when it is accompanied by other degenerating influences, and is acting upon a people already deteriorated. It is, perhaps, for this reason that it produces such disastrous results when consumed by savage or semi-savage races, seeing that it then acts in conjunction with surrounding circumstances upon a people without much resisting power.

Not only alcohol and syphilis, but any other depressing agent or toxin, such as that of influenza, malaria, or other microbial disease, may produce a similar result. All these constitute the "internal environment" of the individual. They are just as efficient in lowering his development as are dismal surroundings, starvation, overwork and so forth.

But obviously something more is needed beside environment to produce infantilism. The causes which have just been mentioned are in action everywhere around us. But in spite of them people grow up well developed and live to a good old age. And even when many of them exist together, the accumulation rarely gives rise to true infantilism, though it may be responsible for some inferiority of height or weight, or length of life. It is, therefore, patent that some other factor is present before definite infantilism can appear.

This other factor is an innate tendency to the particular form of variation (reversion) of which infantilism is the concrete expression. Existing in different people to different degrees, this tendency, if present at all, is usually very slight, but sometimes it occurs to such an extent that, if the conditions of life be suitable, the latent tendency becomes patent and the *minor variation* of infantilism results.

This leads up to the second subdivision of developmental or

individual infantilism. Evolutionary infantilism is the result of environment alone. Developmental infantilism in its more common, or minor, form, to which we have just alluded, is the consequence both of environment and of reversion. The second form of developmental infantilism, to which we now come, has apparently nothing whatever to do with environment but is solely the result of reversion. It is an example of that particular form of variation which we have before referred to as *major or discontinuous*. It is a mutation, sport, or freak, and occurs where some structure or quality of the organism spontaneously harks back to a condition which existed in remote antiquity. It consists, in this case, in the reversion of the individual to the primitive or infantile type. This form of infantilism necessarily arises without any apparent cause, is of marked degree, and is prone to run in families. It is the kind which we have termed "ateleiosis."

The Two Types of Infantilism.

Before going on to deal with the different varieties of infantilism it is necessary to say that French writers recognise two distinct types. One of these is Brissaud's, or the myxœdematous type,* so called because it is believed to be invariably due to thyroid inadequacy, though the characteristic features of myxœdema may be very slight. The sexual organs are also conspicuously infantile, and the osseous and general development are very backward.

The other, *Lorain's*, or the anangioplastic type, has many different causes, all of which are supposed to act upon the vascular system in the first place, delaying or stopping its development. Though the development of the sexual organs may be behind the general development, as a rule they keep pace with that of the body, and may even go a little ahead of it. Ossification is not hindered, and may even be somewhat advanced.

Though these types are quite distinct, it is recognised that there are all sorts of intermediate or transitional forms.†

While acknowledging the value of a recognition of these two types there are objections to making use of them as a basis of classification.

* 'Leçons sur les maladies nerveuses,' Paris, 1895, p. 606; "L'Infantilisme myxœdémateux," 'Nouv. Iconograph de la Salpêtrière,' t. x, 1897, p. 240.

† For example, the case published by Drs. Dupré et Pagniez under the title of "Infantilisme dégénératif (type Lorain) compliqué de dysthyroïde pubérale (type Brissaud)," 'Nouv. Iconograph de la Salpêtrière,' t. xv, 1902, p. 124.

Thus it is by no means clear that the state of the thyroid gland is always the dominating factor in Brissaud's type. Cases have been recorded as of this kind in which sexual and skeletal hypoplasia have been present, and some of the cardinal symptoms of myxœdema entirely absent. Moreover, beneath the cover of fatness, which is a feature of this type, we must not overlook the cardio-arterial hypoplasia which often exists as well. In fact, in some cases described as of Brissaud's type the arterial system is quite as defective as the thyroid. So also in regard to Lorain's type there is evidence that there are other avenues for the production of this form of infantilism besides that of the cardio-arterial system.

We regard ordinary infantilism as a morbid condition which may be set up by many causes. It is never impartial, but is almost necessarily of unequal distribution, so that some organs are more backward than others.

And, just as in old age, the important organs first to degenerate are usually the cardio-vascular, the sexual or the thyroid, so also in infantilism these same organs are often the first to lag behind, but may occasionally be preceded by the pancreas, liver, brain, or indeed, any other organ.

The chief divisions of general infantilism are, therefore :

I. Evolutionary, or racial

II. Developmental, or individual.

A. *As a minor, or continuous, variation :*

(a) Adaptative.

(b) Correlative.

B. *As a major, or discontinuous, variation : ateleiosis.*

C. *Thyroid.*

II

I. EVOLUTIONARY OR RACIAL INFANTILISM

Evolutionary infantilism occurs when the individual and his ancestors have lived for many generations in circumstances calculated to produce developmental stagnation.

THE periodicity, or rhythm, which we have noticed as a striking feature of individual development is equally conspicuous in the development of races. This periodicity is the inevitable result of inequality of progress, whereby one race or nation becomes superior to other races or nations. It is the opinion of some ethnologists, and of De Quatrefages in particular, that parts of the continents of Europe, Asia, and Africa were at one time inhabited by a race or races of broad-headed, short-limbed, swarthy people, who lived in caves or primitive huts of the rudest possible description. The evolution of this prehistoric people of low stature in all probability remained almost stagnant for a vast number of years. They were then overwhelmed by the incursions of a race or races of a bigger, stronger, coarser stock, whose evolution, from climatic and other causes, had proceeded along different lines. It therefore came to pass that in process of time the greater part of these three continents was inhabited by people of long-headed, fairer type, taller and of greater intelligence, and by a more primitive, dwarfish people who were either subject to them, or only maintained their freedom by dwelling in mountains, islands, forests, and deserts. A similar state of affairs occurred in America, as is evidenced by the contents of burial mounds. Indeed, it is conjectured that the fashion of compression of the head so prevalent among some North American Indian tribes had its origin in the superiority of the long-headed, ruling race over the broad-headed people among whom they lived, leading to the imitation of the peculiarities of the former by the latter.*

* See 'Prehistoric Man,' by Dr. Wilson, 1876, p. 151.

Under these circumstances modern experience makes it pretty evident that the influence of the superior upon the inferior races was eventually the complete predominance of the superior. This would be brought about partly by intermarriages and absorption, and partly by extermination, the inferior tending to become still more inferior (degenerated), and ultimately to die out.

We write of this state of affairs as if it were prehistoric and had long ceased. But as a matter of fact these identical changes are still going on. The fusion of the contrasted races is as yet incomplete, and when those of lower development have been able to isolate themselves in some secluded or inhospitable district they have not only escaped extinction, but have remained permanently of low type, and in all probability much as they were in the pre-historic stone ages. They are, in truth, still in the infantile or childhood stage of phylogenetic development.

Of such a kind are the negritos of Asia and the negrillos of Africa, chief among whom are the Akkas, the forest dwarfs of the Upper Congo, the natives of the Andaman Islands, the Aetas of the Philippines, the Samangs and Sakais of the Malay Peninsula, and the Kimos of Madagascar. The natural result of this evolutionary repression is that there is some similarity between them in their adult stages and the more civilised races at an infantile or childish stage of development.

Haeckel divides savages into three orders—lower, middle, and higher—of which the negritos and negrillos are the “lower savages approaching nearest to the apes, pygmies of small stature, four to four and a half feet high (rarely four and three quarters); the women sometimes only three to three and a half feet. They are woolly-haired and flat-nosed, of a black or dark-brown colour, with pointed belly, thin and short legs. They have no homes, and live in forests and caverns, and partly on trees; wander about in small parties of ten to forty persons, quite naked, or with just a trace of some primitive garment.*

De Quatrefages† says that the pygmy people of the present day are everywhere looked upon by their neighbours as inferiors. In India they are termed “the men of the jungle,” or bandar-log, that is, “monkey-people.” “In Borneo the Dyaks chase the negritos

* From ‘The Wonders of Life,’ by Ernst Haeckel, transl. by Joseph McCabe, p. 129.

† ‘Les Pygmées,’ transl. by Prof. Starr. De Quatrefages’ view on the anthropological position of the Pygmy race was also held by Sir W. H. Flower, and has lately been elaborated by Dr. P. W. Schmidt, of Stuttgart, ‘Die Stellung der Pygmaemöller in der Entwicklungsgeschichte des Menschen.’

like wild beasts, and shoot with the blow-gun at the children, who take refuge in the trees—as they would at a monkey.” These dwarf people invariably live in regions into which their enemies do not care or are afraid to penetrate, and are in every case the aboriginal inhabitants. They are always strikingly different from the nations by whom they are surrounded, though they seem to come from the same stock.

They resemble children in many respects. They are all short, those of the Congo measuring about 1·3 m., and others very little more. They are not so prognathous as the negroes, but have faces which are in some respects like those of apes and in others like those of children.

Sir Harry Johnson* draws attention to the presence of certain simian characters in the Congo pygmies. Among them are “the relatively flat tip to the nose and the great development of the nostrils, which are sometimes as much raised above the surface as the tip of the nose itself.” Other similar features are the flatness of the bridge of the nose, the width between the eyes, the “very long and ape-like upper lip,” and the persistence of the fœtal-down or lanugo. “They are almost equally agile with the anthropoids in the climbing of trees.” Their heads are short and broad, though in most cases the people by whom they are surrounded are dolichocephalic. Their bodies and limbs have rounded outlines, and their hands and feet are small. They also resemble one another much more closely than do the adult individuals of more advanced races. Of the Andamanese, it is said that “it is impossible not to be impressed by the uniformity of physiognomy common to nearly all.”† It will be noticed that most of these characters are infantile characters.

Elsewhere‡ these same dwarfs (mincopies) are described as having “huge disproportioned heads, high shoulders, small limbs, and protuberant stomachs. . . . Their habitations are branches of trees spread over four short poles; their couches are leaves, and they have no vessels capable of resisting the action of fire. . . . Their mode of running up a cocoa-tree is remarkable—running up like a monkey and descending with astonishing velocity. . . .” The mincopies are said to have small and delicate hands and feet. “They are active and vigorous, but short-lived.”

Stuhlmann describes the Akkas as “averaging 1·25 m. in stature, with light-brown skins tinged with reddish-yellow. They

* ‘Pall Mall Magazine,’ vol. xxv, 1902.

† ‘Les Pygmées,’ p. 78.

‡ ‘History of India,’ by James Grant, vol. ii, p. 378.

have a round head, flat nose, prognathic face, and woolly brown hair. The beard is scanty, but a growth of light down-like hair covers the whole body. . . . They are cunning and cruel, with thievish propensities and many childish traits.”*

We can hardly expect that all these ape-like or child-like features should be presented together in each individual or even in each tribe, but rather that some should be more prominent in one and



FIG. 19.—From ‘The History of Mankind,’ by Ratzel. Though of adult development the physiognomy contours and proportions are all childish.

some in another. The African negrillos are often pot-bellied, their heads are large in proportion to their bodies, and their lower limbs are short, so that their general proportions greatly resemble those of undeveloped human beings (children) of the higher races. But their undeveloped condition is most conspicuously indicated by deficiency in the secondary indications of sex. So also “among all Andamanese, men or women, the body is nearly of uniform width, and scarcely enlarged round the hips and trochanters.” The men rarely

* Prof. Starr, “Pygmy Races of Man,” ‘North American Review,’ 1908.

have any trace of beard, and among negritos and negrillos in general sexual hair is not abundant. On the other hand, some of them are more than usually hirsute in other respects. As we have seen, Sir Harry Johnson says that in some of the Congo dwarfs the lanugo of babyhood persists through life, and Du Chaillu* observed of the Obongos, the forest dwarfs with whom he came in contact, that the men were remarkable for having their breasts and legs covered with hair.

Emin Pasha† remarked of some Akkas he examined that the whole body was covered with hair, and that this hair was stiff and exceedingly thick, and in some cases even felted.

Now it is evident that two or three circumstances stand out very clearly in connection with these people. The first is that they are of a very low order of development, approaching the anthropoid apes in form and character. In the second place they are to all appearance stationary or nearly stationary in their development. In the third place they owe their stagnation to their surroundings, for they are always located, as De Quatrefages insists, "in the least favourable localities of the country where they live" (p. 24). They represent the backwash of the evolutionary stream, and may be regarded as examples of racial infantilism, for they seem to represent the infant stage of the evolution of man, and owe the persistence of their type to a stagnating environment.‡

Tyson in his 'Anatomy of a Pygmie,' a "Philological Essay concerning the Pygmies of the Ancients," § transcribes a passage out of Photius giving an account of the travels of Nonnosus, "the Emperor Justinian's ambassador," into Æthiopia.

"That *Nonnosus*, sailing from *Pharsa*, when he came to the farthestmost of the Islands, a thing, very strange to be heard of, happened to him, for he lighted on some (*Animals*) in shape and appearance like *Men*, but little of stature, and of a black colour, and thick, covered with hair all over their Bodies. The Women, who were of the same stature, followed the Men. They were all naked, only the Elder of them, both Men and Women, covered their Privy Parts with a small Skin. They seemed not at all fierce

* Rev. J. G. Wood, 'Natural History of Man,' vol. i, p. 538.

† Prof. Ratzel, 'The History of Mankind,' transl., div. iv, p. 303.

‡ The Bantu and Negro races are also in a state of racial infantilism, but it is not so much the infantilism of stagnation as of degeneration. They are derived from a stock superior to themselves, whereas there is reason to believe that the dwarf races come by a protracted line of descent from an inferior stock.

§ Written in 1699, edited, with an introduction treating of pygmy races and fairy tales, by Professor Windle, p. 29.

or wild, they had a Humane Voice, but their *Dialect* was altogether unknown to every Body that lived about there, much more to those that were with Nonnosus. They liv'd upon Sea Oysters, and Fish that were cast out of the Sea, upon the Island. They had no Courage, for seeing our Men, they were frighted, as we are at the sight of the greatest wild Beast."

III

II. DEVELOPMENTAL INFANTILISM

General infantilism occurs as a minor variation when the environment is calculated to retard development, and there is at the same time an inherent tendency to regress. The depressing environment may be either external or internal.

A. Infantilism as a Minor or Continuous Variation.

WE have seen that there is a normal relation between the human body and its normal surroundings, with the result that the degree of development of any organ or part bears a certain relation to every other organ and part. In health this relation is not fixed or rigid, but is exceedingly variable. A process of adjustment is continually going on whereby each organ which exceeds or comes short of its proper proportions is made to conform to the common standard. This adjustment or *adaptation* produces normal results when the circumstances are normal, and abnormal when circumstances are persistently or grossly abnormal.

We have also shown that, as the result of innumerable adjustments, certain organs become so habituated to act together that when one of them breaks down from failure or acceleration of growth or development, an *associated* or *correlated* organ is liable to follow suit.

Furthermore, what is true in these respects of organs is also true of the whole body. In other words, general infantilism is the result of adaptation to abnormal surroundings or correlation to some abnormal organ.

Hence infantilism as a minor variation may either be—

- (1) Adaptative, or—
- (2) Correlative.

Any classification founded upon aetiology must of necessity be very rough and inaccurate, because of the difficulty of distinguishing between cause and effect. Thus in regard to the infantilism associated with cirrhosis of the liver, one will look upon the infantilism as the origin of the cirrhosis, another will reverse the order and put the cirrhosis in the first place, and much the same may be said of other examples of infantilism.

There may be more than one cause. Sometimes the local disorder is primary, and the general infantilism is correlated, or adapted to it. At others the reverse is the case, and the original defect is one of the body as a whole. This is most likely true of the pancreatic, cardiac, arterial, hepatic, and renal forms. It is probable that their relations are variable, so that sometimes the local disease comes first, at others second; to some extent acts as a cause, and to some extent as a consequence.

In some cases the anomaly seems to be produced by correlation alone, as in the association of cirrhosis of the liver with splenomegaly in Banti's disease. But more often the causes are mixed, as when the spinal cord undergoes a peculiar form of degeneration in pernicious anæmia. We are then strongly inclined to take the view that the local is in part the direct product of the general disorder.

I. Infantilism the Result of Minor Variation and Adaptation: Symptomatic Infantilism.

Under this heading we include not only those cases due to defective sanitation in general, but to fevers, syphilis, alcohol, and other forms of intoxication.

This must be obvious when we consider that the stifling air, bad food, and dark hovels, which are such a fertile source of defective development in slum children, largely produce their effects by the poisoning to which the re-breathed air, the rotten food, give rise, to say nothing of the alcohol and fevers which so often go with them.

No one who has had much experience of infantilism can fail to observe that cases occur in which so many causes have been at work that it is not possible to attribute them to one cause in particular. On the other hand, the action of alcohol, syphilis, or other poison, though not, strictly speaking, that of an environment, is so in reality, for it is the outcome of surroundings, and there could be no intoxication unless these circumstances were favourable.

But though no real distinction can be made between the actions of unhealthy surroundings and of poisons introduced from without, yet it is more convenient to separate the two.

Adaptative infantilism may therefore result either from—

(a) Insanitation (unhealthy surroundings) or—

(b) Intoxication.

(a) **Infantilism of insanitation.**—Defective general development due to bad air, defective food, absence of sunshine, and allied circumstances, is probably more common than is supposed. The

very familiarity of these causes and their multiplicity stand in the way of their recognition, so that though we all agree in holding them responsible for stunting growth and development, they are seldom, if ever, acknowledged as the cause of specific cases of infantilism; yet that these indefinite causes do account for infantilism there can be hardly any doubt. They act so insidiously that we are far less likely to recognise the impression that is made than when some more definite and less intangible cause is at work. Hence a case of infantilism which is in reality due to bad sanitation in general is seldom attributed to that cause, but is put down to scrofula, measles, scarlet fever, whooping-cough, and some other illness which has cropped up incidentally out of the general level of unhealthy life, though the illness may in reality have had very little to do with the infantilism. We have ourselves seen in the Woodley convalescent home for children, and elsewhere, cases of infantilism derived from London slums for which it is impossible to find any one adequate cause.

(b) **Toxic infantilism.**—Nevertheless infantilism as the result of bacterial intoxication is by no means uncommon. It is met with as a consequence of enteric fever, scarlet fever, diphtheria, influenza. In brief, any form of intoxication may lead to morbidly defective general development. Thus, not only the disorders mentioned, but the toxins of syphilis, of tubercle, of wine, and of tobacco are all either known, or suspected, to be important agents in hindering progressive development and causing infantilism.

It is necessary, again, to insist that seldom, if ever, does any particular cause, or combination of causes, alone give rise to genuine infantilism. Probably circumstances and inborn tendencies always work together.

Though the *infective fevers* are fruitful sources of impaired development, they seldom go to such lengths as to produce veritable infantilism. But this occasionally happens, as in the following case, though the exact nature of the intoxication was not discovered.

Dr. Schmidt,* of Munich, describes an instance in Theresa Fend, a girl, aged 16 years, who was of normal size for the first half of her life, and in her ninth year was in bed for a fortnight with a severe illness, of which no details were obtainable.

From this time growth almost ceased, and at most did not amount to more than 2·5 or 5 cm. When Dr. Schmidt saw her at the age of sixteen years she had the appearance of a child of eight, this being the time at which she first gave evidence of delayed growth. The

* 'Zur Kenntniss des Zwergwuchses, Arch. f. Anthropol.,' Bd. xx, 1891, S. 59.

grandparents and two sisters were of normal size. She was not microcephalic, but, on the contrary, was of good intelligence, well-proportioned, and of good muscular and fatty development. She had broad shoulders, a well-formed thorax, and healthy lungs. There were no signs of the approach of puberty. The abdomen appeared to be inflated with gas, but there was no abdominal tumour nor ascites. The teeth were of the permanent set, though the canines of the right side were only just appearing through the gum. They first appeared in the sixteenth year. The other teeth appeared to be normal. Five molars were erupted, and three others seemed to be about to break through. Her height was 1160 mm., the height of an average girl of her age in Bavaria being 1520 mm. A photograph of the girl is given with the article.

Rheumatic fever.—We are indebted to Dr. Bascombe, of Saffron Walden, for the following case :

L. K—, aged 32 years, was one of a family consisting of the parents and four sisters, all of whom were of medium height. She had rheumatic fever at thirteen, but could not speak as to what her health had been prior to that time. Her height was 115·7 cm., and the circumference of her head was 53·2 cm.

The general configuration of the body and face were good, and the proportions were like those of an adult. The thyroid gland was apparently normal.

The lower end of each ulna was dislocated backwards, so that the hand was thrown laterally to the ulnar side. This was undoubtedly a pre-natal deformity.

There was a scarcity of axillary and pubic hair. The pelvis was well formed and actually, but not relatively, small. Breast-tissue was present, but breast and nipple were both of childish size. The generative organs were small.

This patient was certainly of defective intelligence, but by no means imbecile. She might be considered a good example of Lorain's type of infantilism, though we could not assure ourselves that there was any disproportionate hypoplasia of the heart or blood-vessels.

Tobacco infantilism.—There is evidence that tobacco is a cause of arterial sclerosis (see p. 351), and therefore of premature senile decay. We have also seen that, generally speaking, those causes which accelerate the declining periods of development and give rise to senilism hinder the rising periods and bring about infantilism. So that, arguing from analogy, there is good reason to regard tobacco smoking as a cause of the stunting of growth.

Professor Sims Woodhead* says that "smoking interferes with the development of the growing child," and mentions some observations made among the students at Yale University extending over a period of eight years, tending to show that smokers do not develop at the same rate as those who do not smoke.

Nevertheless, we cannot find any really satisfactory case of actual infantilism produced by tobacco. The nearest approach to infantilism is recorded by Hertoghe,† who writes of two cases of "chronic intoxication with tobacco" in youths causing infantilism. In neither case was the height or weight reduced below the limits of normal variation, the infantilism being mainly of the sex organs, which are described as "infantile." There appeared to be no symptom of thyroid inadequacy nor of defective intelligence, yet the administration of thyroidin was followed by increase of growth, so that in one case nearly 2 cm. were gained in thirty-three days. In both cases there was thinness with pallor, and the brothers and sisters who did not smoke were of normal height and in good condition.

It cannot be said that the evidence for these being regarded as cases of infantilism is very convincing. Moreover, the very slight increase in height which took place when thyroidin was given was scarcely enough to prove a pathological degree of thyroid inadequacy. It seems not improbable that the tobacco produced an impairment of development of all-round character, affecting the thyroid gland, not primarily, but simultaneously with every other organ.

Infantilism from chronic intestinal infection.—Professor Herter, in a book bearing the above title, has drawn attention to the importance of intoxication due to "overgrowth and persistence of flora of the nursing period" in giving rise to infantilism. This is based upon the careful study of five cases, and less detailed observations of five more.

This infantilism is not associated with any sign of mental deficiency, but a moderate degree of anæmia and a flabby condition of the muscles seem to be constant features. There is marked abdominal distension, with occasional bouts of diarrhœa, usually mild in degree and of short duration. The appetite may be good or even voracious.

"The movements are voluminous, gray or light brown in colour, and of sufficiently low specific gravity to float on the surface of water." They are usually formed, but soft and of a sour odour, and are excessively fatty, and often contain casein-like masses of soap.

* 'The Medical Temperance Review,' 1906, p. 551.

† 'Bulletin de l'Académie Royale de Médecine de Belgique,' October 30th, 1897.

There is even greater intolerance of carbohydrates than of fat, so that nothing brought on the digestive disturbances so effectually as slight indiscretions in the giving of starch foods.

The motions contain a large and varied assortment of bacteria, mostly Gram-positive organisms of the *Bacillus bifidus*, *Bacillus infantilis*, and of the coccal types. The urine contains "an excess of putrefactive products of intestinal origin. Prominent among these are indican and phenol compounds."

Herter ascribes the infantilism to defective nutrition, the result of chronic inflammation in the ileum and colon, associated with the presence of abnormal forms of bacteria. He claims that careful dieting and general hygienic supervision, based upon this theory, lead to re-establishment of growth, but that relapses are common, and in severe cases a permanently undersized individual is inevitable.

Professor Herter does not allude to the pancreas as a possible source of the trouble in these cases, though some of the symptoms are highly suggestive of pancreatic inadequacy, and makes no reference to other causes of infantilism.

The following seems to be an example of this form of infantilism. We at first regarded the case* as one of "normal infantilism" owing to the apparent absence of cause, though the defective development was evidently of a minor description. But Dr. Byrom Bramwell, in referring to it, very rightly objected to the application of the word "normal" to any kind of infantilism. The word ought, indeed, to be reserved for a disease process. We are now inclined to take the view that the infantilism in this case was partly the result of intestinal troubles, but whether of pancreatic origin or not we cannot say. These were referred to when we first saw the girl, but only in a casual way, as to an ailment, of no particular importance. But, on subsequently referring to this subject, it appeared that she had had many such attacks, and that they dated back to early childhood. Moreover, the motions were sometimes large and offensive and pale in colour, though, as a rule, there was nothing noticeable about them. At the time we saw her she was just recovering from an attack. The mother was quite clear in her statements that there were often long intervals during which there was no flux and the motions were normal.

We are indebted to the Drs. Keith for this case, which was that of a girl of fifteen years and a half, whose stature was no greater than that of a girl of six, whose ossification and dentition corresponded with that of a girl of eleven, and whose sexual develop-

* 'Practitioner,' vol. lxx, 1903, p. 817.

ment was not more advanced than that which is usual at twelve. There was no special type of face, and the girl resembled her mother in appearance. The proportions of the body were adult rather than childish, the middle point being at the pubic symphysis, while the extremities were comparatively long. The intelligence was fully equal to that of most girls of her age. Though the condition had



FIG. 20.—*Intestinal (?) infantilism*: Girl, aged 15½ years (on the right) compared with normal girl, aged 5½ years. There is no special type of face, and the delay of development is neither abrupt nor very conspicuous. Note that in this case, though the stature is about ten years behind, the carriage, facial expression, proportions of the body, and development of the pelvis and sexual organs are not far short of those which are usual in girls of her age.

first been noticed when she was between two and three years old, the delay of development was not very pronounced and above all, the pelvis and sexual organs were by no means infantile.

Alcoholic infantilism.—Nothing seems to be better established than the fact that alcohol is an important cause of premature old

age, no matter whether it be of cells, of organs, or of men, and there is consequently good reason to infer that it is also a prolific source of defective development. There is a common impression that gin, or other spirit, taken in early life, hinders or stops growth, but singularly little definite evidence exists upon the subject. In all probability the impression referred to is to a large extent founded upon experiments upon dogs carried out at Bologna. These dogs were made to drink *eau de vie* and wash in spirit, after having their hair shaved off, with the result that their development (or growth) was seriously delayed.*

In 1896, Dr. Lancereaux,† at a meeting of the Académie de Médecine, brought forward two cases of defective development in children, said to be due to the consumption of alcohol. One was in a child of nine. The second was in a child of fourteen years, who, since she was two years old, had taken from a pint to a quart of wine daily, with the result that her development was like that of a child of six. In spite of removal of the cause neither of these children seemed to improve in development. But it is impossible to regard these as cases of alcoholic infantilism, seeing that in the one case there had been typhoid fever at nine followed by pneumonia and empyema, and in the other there was ascites with enlarged heart, liver, and spleen; so that the infantilism may have been due to these causes as much as to, or, indeed, instead of, the alcohol. It was probably of mixed origin.

Syphilitic infantilism.—Just as one of the symptoms of syphilis in the adult is a haggard careworn aspect, with emaciation and appearance of premature age (*cachexia syphilitica*), so the same toxin acting upon man in the early progressive stages of his development will impair development and produce infantilism.‡

While general intoxication with syphilis is responsible for many cases of infantilism, this effect on development is greatly accentuated by the local degenerations to which the disease so often give rise. Thus Fournier says that the infantile form of this disease often causes lesions (defective development or fibrosis) of the testes, leading either to sterility or to impaired virility. Infantilism, or premature degeneration, of the ovaries, or other organs, may also contribute. In the third part of this book we have alluded to some of these syphi-

* 'Dict. Sci. Med,' vol. xxxv, article, "Nain," p. 149.

† 'La Presse Médicale,' vol. iv, 1896.

‡ E. Fournier, 'Recherche et Diagnostic de l'Hérédo-syphilis tardive,' 1907; also A. Fournier, 'La Syphilis héréditaire tardive,' 1886.

litic and parasyphilitic affections of the liver, kidneys, and other organs.

It is important to remember that the infantilism produced by syphilitic and other intoxications is a minor variation, and is therefore not transmitted to descendants. Sir Jonathan Hutchinson, in the fifth volume of his 'Archives,' refers to a woman rendered dwarf and deaf by inherited syphilis, who was the mother of a boy who grew up into a well-developed man, taller than herself.

IV

GENERAL INFANTILISM OCCURRING SOMETIMES AS A MINOR AND SOMETIMES AS A MAJOR VARIATION : CORRELATIVE INFANTILISM

Morbid defect of development may result from correlation of the whole body to the standard set by an infantile or degenerated organ. In such cases it may be difficult, even impossible, to say whether the general infantilism is major or minor.

WHEN general infantilism is preceded by defective development or premature degeneration of some important organ it may be very difficult or impossible to say whether it should be regarded as a minor or as a major variation. In some cases the major character of the variation is settled by the occurrence of heredity, and in others the obvious action of a cause may make it equally obvious that the variation is minor, but there are many cases in which the nature of the variation is not so apparent. Hence it seems most fitting that correlative infantilism should be placed in a chapter by itself between the minor and major forms.

II. Correlative Infantilism.

Infantilism the Result of Variation and Correlation.

One of the best instances of correlative or induced infantilism of minor degree is that which is the result of *Pott's disease* of the spine. In this malady, particularly if it occurs during infancy or early childhood, some degree of infantilism is not uncommon. Drs. Pierre Marie and André Leri call attention to this fact,* and point out that the infantilism is of the Lorain type the limbs being relatively long and the head small. They also say that the genital organs are usually of more advanced development than the rest of the body, but are occasionally defective.

The late Dr. Bryant on one occasion told us that he then had under his care in Gny's Hospital a young man of twenty-one who

* 'La Presse Médicale,' vol. xii, 1904, p. 191.

was affected with *muscular dystrophy* and was a well-marked case of infantilism, the general and sexual development corresponding with that of most boys of about thirteen or fourteen.

Infantilism may also go with *scleroderma*. In a case of this description described by M. Platon there was pre-natal atrophic sclerosis of skin and muscle, with wasting of the underlying bone. M. Platon attributed it to congenital syphilis. The patient was 28 years of age, but looked no more than twelve, was 1.45 m. high, and weighed 24.035 kg. There was the usual tight, wasted skin of scleroderma, and extreme muscular emaciation. The ears were thin and hard, and destitute of lobes. With the exception of a few downy hairs on the cheeks and chin there was no facial nor body hair, though that on the head was fairly abundant. The cranium was relatively big and was dolicephalic, with prominences of bone here and there, a notable projection of one mastoid process, and a definite exostosis of the other. The anterior fontanelle seemed to be imperfectly ossified. The description reminds one of progeria (p. 649) which it resembles in many respects.

Hepatic and Splenic Infantilism.

Hasenclever* records the occurrence of three instances of hypertrophic cirrhosis of Hanot's type in one family, all of them associated with defective general development. Their heights were—(1) aged 24 years, 1.58 m.; (2) aged 22 years, 1.49 m.; (3) aged 18 years, 1.40 m. There were two other children without cirrhosis, and of normal development.

Gilbert and Fournier† give an account of a youth of nineteen, whose height and weight were very inferior and sexual system undeveloped. Hypertrophic cirrhosis was first noticed at seventeen, but the general development was only equal to that usual at fourteen or fifteen.

They also describe a group of cases of infantilism associated with splenomegaly, bone changes, pigmentation of the skin, enlargement of the liver and jaundice.

It is probably an example of this disease which was brought before the Brighton division of the British Medical Association in 1905.‡ The patient was aged 26 years, but his height was only 4 ft. 11 in. (149 cm.), and weight 4 st. 8 lb. (3 kg.). He had an

* 'Berlin. klin. Wochenschr.,' 1898, Bd. xxxv, S. 997.

† 'Rev. Mens. des Maladies de l'Enfance,' 1895, p. 39.

‡ 'Brit. Med. Journ.,' 1905, vol. i, p. 1272.

enlarged spleen and liver, and there was pronounced general infantilism, though the mental condition was normal. There was said to be "no sexual development." The blood-count showed 1,120,000 red corpuscles and only 11,000 whites per c.mm. including 6 per cent. of myelocytes. The hæmoglobin was 15 per cent.

Lereboullet* gives an instance of hypertrophic cirrhosis in a boy of fifteen whose height was about equal to that of his normal brother of eleven and a half.

Cardiac and Arterial Infantilism; Anangioplastic Infantilism; Mitral Infantilism.

No organs in the body are of such vital importance in animal mechanics as the arteries. We have seen that the degeneration of many organs dates from the failure of their arteries, and in old age general existence hangs upon the same threads, for sudden death or paralysis by rupture or blockage of a cerebral artery is one of Nature's favourite methods of happily ending life which has ceased to be useful. Hence the dictum that a man is as old as his arteries. Next to the arteries the most natural and merciful termination is by gradual or sudden cessation of the heart's action, either through slow interference with the cardiac centre or by fibrosis or molecular deterioration of the heart itself.

It fits in with our conception of infantilism and its relations with senilism that while premature senility so often depends upon arterial degeneration, so also defective development of the heart or arteries is the pivot of many cases of infantilism. But this no more means that the infantilism is *caused* by a preceding defect of development of these important organs than that old age is due to their degeneration. All that we are justified in saying is that in both cases the arterial or cardiac changes are a little anterior in order of time. In arterial sclerosis (arterial senilism) senile changes are usually going on elsewhere, but are perhaps a little more advanced in the circulatory apparatus. So also in infantilism the entire body is of defective development, though the defect is most conspicuous, and perhaps antecedent, in the heart and arteries.

But sometimes the circulatory defect is notoriously in front of the general infantilism, and may reasonably be suspected of being largely responsible. It is these cases in particular which comprise the anangioplastic variety of infantilism, of which the following are examples. They correspond with those cases of premature senility

* "Un cas de cirrhose biliaire anictérique," 'Soc. de Pédiatrie,' April 9th, 1901.

in which the heart or arteries are seriously degenerated, while in all other respects the body is still young.

Dr. Lacomme* gave the name of "mitral infantilism" to a case recorded by him in 1899. The patient, a woman, aged 24 years, was 1.56 m. in height, chlorotic, easily tired, and with poor digestion. She had first menstruated at sixteen. When eighteen she had syphilitic pigmentation of the neck, and mucons patches on the vulva. The uterine and external genital organs, both primary and secondary, were of infantile development, but there were a few pubic hairs. There was a pre-systolic murmur at the apex.

In this case the syphilis was apparently of the acquired variety.

Dr. Luigi Ferrannini† reports the case of a young man, aged 22 years, with the development usual at thirteen or fourteen. He had a timid, feminine expression and a childish voice. The sex organs as well as the mental and psychical characters were also childish. There was evidence of mitral stenosis.

Girandean‡ gives an account of three patients with generally defective development of the body, in one of whom there was congenital heart disease associated with malformation of the sternum.

Dr. Sutherland's§ case was that of a boy, aged 11 years, 28 lb. (12.69 kg.) in weight, and 39 in. (99 cm.) high, who showed clubbing and blueness of his fingers and backward intelligence.

Infantilism associated with Raynaud's phenomena.—We are indebted to Dr. Styles, of Moreton-in-the-Marsh, for this case.

The patient was a youth, aged 17 years when we first saw him. He is said to have stopped growing when twelve years of age, after a feverish attack of one week's standing, but this attack was preceded by measles and by diphtheria. The family history was uneventful. He favours his mother in appearance.

He is thin, but of good proportions, is 1.33 m. high, has a head circumference of 54.4 cm., and is of average intelligence. The thyroid gland seems to be normal, but the sexual system is of backward development. Though the testicles seem to be of a size usual to a boy of his age there is no growth of sexual hair anywhere.

The heart appears to be of normal size and no murmur can be detected, but he sometimes complains of pain in the cardiac area running down the left arm.

* "Rétrécissement mitral avec peu d'infantilisme," 'Loire Médicale,' 1899, p. 63.

† 'Riforma Medica,' 1900, pp. 162, 375, 687.

‡ "Rétrécissement mitral et Hystérie chez l'homme," 'Arch. générale de Méd.,' s. vii, tome 26, p. 547.

§ 'Lancet,' 1905, vol. ii, p. 1036.

The pulse is small and regular. His hands and feet are usually cold, and sometimes the fingers become pale and livid, as if the circulation had stopped. We saw him on one occasion when his fingers were in this condition, and noticed that the arterial hyper-tonus was that characteristic of Raynaud's disease. All the fingers



FIG. 21.—*Anangioplasic infantilism*: A youth, aged 17 years, standing beside a man of ordinary stature. His height corresponds with that which is usual at ten, and he is also backward in sexual development, but his physiognomy and proportions are more advanced.

were cold and waxy, and this condition, after lasting for some hours, gradually gave place to one of redness and warmth. The attacks are induced by cold and by mental disturbance, but are usually more or less capricious or irregular.

Infantilism Originating in Anomalies of the Central Nervous System: Cerebro-spinal or Neuropathic Infantilism.

Another important series of organs to fail at an unusually early age of regressive life and to lead all other organs along the road to ruin is the cerebro-spinal. The brain especially is apt to degenerate early, leading to dotage or dementia before other parts of the body are beginning to degenerate.

So also is it with the same system at infantile or progressive periods of development. In some cases of defective development the most conspicuous feature is the impaired intelligence, or even imbecility, with which it is accompanied. Generally speaking, when we see a case of infantilism in which the imbecility is the most con-



FIG. 22.—*Symptomatic infantilism: showing absence of special physiognomy.*

(1) Intestinal infantilism. (2) Dr. Williams's case of infantilism with defective intelligence. (3) Dr. Bramwell's case of pancreatic infantilism. See also figure of anangioplasic infantilism on opposite page.

spicuous feature, we are probably right in terming it "neuropathic." The form assumed is that of Lorain's type as a rule, but it is by no means certain that some instances of Brissand's type with defective intelligence ought not to come under this heading, for it does not follow that the imbecility is necessarily due to incipient cretinism. The infantilism and imbecility may be merely correlated.

Hydrocephalus is sometimes associated with infantilism, as in a case described by Dr. Barnes in 1848.* The hydrocephalus began at the age of six months, and at the age of nine years the "form and proportions, as well as the size of the trunk and limbs, were exactly those of an infant of two years old." The patient, a boy, weighed 16 lb. (7250 g.). Dr. Barnes mentions two other cases.

Imbecility.—Dr. E. C. Williams, of Bristol,* showed at the Bristol

* 'Trans. Path. Soc.,' vol. iii, p. 126.

† 'Reports of the Society for the Study of Disease in Children,' vol. iii, 1902-3, p. 248.

Medical Society a girl (see p. 571), aged 10 years, who had not grown since four, weighed 26 lb. (11.79 kg.), and was 3 ft. (91.5 cm.) in height, head circumference $18\frac{3}{4}$ in. (47.4 cm.). She was clumsy and of defective intelligence. Though she knew her alphabet and could count, she was unable to read or to calculate. She would answer simple questions intelligently.

*Microcephalic Infantilism.**

The microcephalic child is usually very backward in its general growth or development. Microcephaly, in short, is one of the causes both of dwarfism and of general infantilism. The reduction in size of the whole body, apparently with the object of bringing it within the compass of the small brain, is sometimes very conspicuous. There is a form of dwarfism seemingly of this kind in which the correlation of all parts of the body to the undeveloped brain is so perfect that at first sight we entirely fail to see that there is any microcephaly at all. In cases belonging to this type it is not the smallness of the head which attracts our attention, but the restlessness combined with the diminutive size of the whole body. Observing a little closer we notice that these individuals have a peculiar physiognomy. In extreme instances the facial features are those typical of microcephalic imbecility or idiocy. The nose is conspicuous, the chin receding, and the whole expression, combined with the contour of the face, reminds one of a ferret or rat. We have been told by an Anglo-Indian judge that within his circuit in one of the provinces of India there was a shrine of some Indian saint at which a number of microcephalic people were kept, and that they went by the name of rats—we believe, “Shah Dowlat’s rats.”

An important factor in the production of microcephalic infantilism is genital deficiency. This is almost invariable, and is shown in corresponding degree in the less pronounced forms. The correlation is, in fact, three sided. The brain is infantile, the sexual organs are infantile, and the next step in correlation results when the whole body is infantile. We then have all the ingredients of general infantilism, produced, not as in ateleiosis, by a primary disposition of the whole body, but by a process of adaptation, whereby first the sexual organs and then the general development are accommodated, by force of ancestral habit, to the requirements of a diminutive brain.

* Microcephaly has already been referred to as an affection of the brain as an organ on p. 323.

The condition arrived at is one of reversion, though the method by which it is attained is somewhat roundabout. As a rare event microcephaly is associated with distinctively simian characters, such as elongation of the forearm or hirsuties.*

We may divide microcephalics into three classes, according to whether the general adaptation is good, bad, or indifferent.

When correlation is very defective the head remains small, but the rest of the body is not particularly undersized, judged by ordinary metric standards of bodily proportion. Even the scalp may not share in the deficiency so that it remains one or two sizes too big for the skull.

When correlation exists to a moderate degree, with a brain of the same weight, the rest of the body is defective in size.

When correlation is good, then the individual is not only dwarfed in his brain, but is correspondingly dwarfed in his whole body.

In the first case, with the same degree of brain defect, the small-headed individual is an idiot, in the second an imbecile, and in the third intelligent.

Let us now give examples of these three grades of microcephalic infantilism.

1. Correlation very Defective: Idiocy.

This is the microcephalic idiot met with in idiot asylums. The head is obviously small, and the rest of the body actually small but relatively large. The forehead slopes backward, the nose is often disproportionately long and projecting, the mandible small and receding. Microcephalics are often nimble, quick, incessantly moving, incapable of fixing their attention upon anything, so that they restlessly glance from side to side, and are far too fidgety to be photographed, unless in a strong light and with instantaneous exposure. They are incapable of speech, but are usually fond of music. They are not only lacking in growth and development, but in nutrition. Their resistance to attacks of micro-organisms is feeble, so that they are liable to acquire pneumonia, bronchitis, or tuberculosis; and, once ill, the disease is prone to run a rapid and unfavourable course, speedily putting an end to their existence.

2. Correlation Defective: Imbecility.

In the middle of the last century two half-breed dwarfs, the offsprings of a Spanish and an Indian parent, were exhibited in London

* Dr. Ireland in the 'Dictionary of Psychological Medicine,' vol. ii, by Dr. Hack Tuke.

as Aztecs and attracted a great amount of attention. A sensational tale was told by their owners of the way in which they had been



FIG. 23.—*Microcephalic imbecility*: The so-called Aztecs. The smallness of the heads is hidden by the bushy hair. In each case the nose is big, the chin receding. The male is club-footed.

discovered, and of the veneration with which they were regarded by the inhabitants of their native district on account of the antiquity of their descent, and models of them were actually made for the

ethnological department of the Crystal Palace. This story deceived a good many scientific people until its falsity was exposed by Prof. Owen, who showed that they were small-headed imbeciles (Fig. 23).

They were able to pronounce a few simple words, were vivacious, restless, and excitable, and were described as hawk-like in facial appearance. The circumference of the head of the male was 381 mm. (15 in.) at the age of forty-six. They were of decidedly short stature, but no measurements are recorded of their height and weight at maturity. They lived into middle age, and their later photographs showed them to have long frizzly hair, originally black, but then white or grey. They are said to have had good health,* and were alive in 1893, when they must have been more than fifty years old.

It was remarked that throughout their lives these imbeciles behaved in every way like children, were sexually undeveloped, and that even in their small vocabulary the words and the manner of using them were childish. The male showed deficiency of the metacarpal bone of each little finger.

3. Correlation Good ; Intelligence Retained.

The following is an excellent example of a microcephalic child in whom the proportions of the body seemed to be so well adjusted to the mental capacity that no imbecility resulted. The case excited some controversy when he appeared before the Anthropological Society of Paris, and we give the gist of the discussion which took place.

Edouard Placereau.—This case was described by Magitot † and by Baron Larrey ‡. He was born in 1867, was a third child, the rest being of normal proportions. He is said to have been so small at birth that he could be “enveloped in a pocket-handkerchief.” At the time he was described he was fourteen years old, 93 cm. high, and well proportioned ; though, at the same time, it is remarked that he was of the height of 6 or 6½ heads, whereas that normal for a child of his age is 5–5½ heads, showing that, owing to the smallness of his head, his general proportion were those of an adult rather than of a child. His weight was 9 kilos. He was said to

* ‘Giants and Dwarfs,’ by E. J. Wood ; Dr F. Birkner, ‘Arch. f. Anthropol.’ Bd. xxv, No. 97, Bd. lxxiii, No. 4 ; Dr. Ireland in Dr. Hack Tuke’s ‘Dictionary of Psychological Medicine,’ vol. ii.

† “Études Anthropologique sur un nouveau cas de Nanisme,” ‘Arch. de Toccol,’ Paris, Tome viii, 1881, p. 660.

‡ “Notes sur un cas de Nanisme,” ‘Bull. Acad. de Méd.,’ Paris, 1881, Qs. x, 1216–18.

be of medium intelligence, equal to that of a child of ten years, and that he could read and write a little, and had a retentive memory.

He was remarkable for the extraordinary volume of his nose, which measured 4.5 cm. in length and 2 cm. in width at the base. The following measurements are given, among others :

Greatest antero-posterior diameter of skull	. 14 cm.
„ transverse „ „	. 12 cm.
Horizontal circumference 39 cm.

Dr. Magitot pointed out that the limbs and their segments were of ordinary proportions, but that the hands presented a low development of the thenar eminences, “a feature nearly always present in microcephalics.”

The genital organs were normal. The teeth (fifteen in number), consisting of seven temporary and eight permanent, resembled those of a child of from seven to eight years of age. Dr. Magitot drew attention to the length of the nose, which caused this dwarf to resemble microcephalic dwarfs, though there was some question whether he had not inherited that feature, for a paternal uncle was said to possess a nose of the same size and form. Moreover, his mental condition did not present any of the lapses or defects of expression observed in microcephalic imbeciles. His psychic condition was said to resemble that of a younger, but ordinary child.

In the discussion which followed the reading of this paper, M. Topinard regarded the nose as characteristic of microcephaly, and contended that the boy was “not only a dwarf but a typical microcephalic.” M. Pozzi thought him a demi-microcephalic idiot. M. Le Borde demurred, and regarded the nose as an hereditary feature, present also in the grandfather. M. Prat noted the continual excitement of the child, so that he was always moving, recalling to him the ways of the dwarf “Princess Pauline,” who “throws herself on the ground all the time.” He did not regard the dwarf as microcephalic. Reference was afterwards made to his “slender, retreating chin.”

Baron Larrey described him as one of the smaller microcephalics, without signs of idiocy. Like many others who saw him, he observed a strong resemblance between Placereau's face and that of the so-called Aztecs, chiefly because of the extraordinary size of the nose. He remarked an “atrophied” condition of the body and limbs of Placereau.

There does not seem to be any room for doubt that Placereau was microcephalic, for the circumference of his head was only 39 cm.

instead of the 43 cm. which Ireland states to be the lower limit of the normal circumference. Moreover, his facial appearance and his restlessness were in favour of the same view. There is good reason to regard him as having defective development of the brain in the first place, and such a perfect adaptation of the size of the limbs and trunk to the low mental standard as to permit of the retention of a fair amount of intelligence.

Placereau apparently belongs to a very pronounced type of infantilism which cannot be accounted for by any of the recognised causes of delayed development. The stature is so small and the proportions so good that these dwarfs are in great demand for the purposes of exhibition in shows.

Our knowledge of these diminutive beings is so imperfect that it is not yet possible to pass a definite opinion on the subject, but we have good reason to regard them as microcephalic in the first place.

The following are a few examples (Figs. 24 and 25) :

CASE 1.—Among the best known was Frank Flynn, or “General Mite,” who was examined by Virchow,* and found to be 80·7 cm. in height, the head being 41·5 cm. in circumference. His head, therefore, as Virchow pointed out, was a little too large for his body (adult standard), though he was in other respects of excellent proportions. When seen by Professors Ranke and von Voit,† one year later, at the age of sixteen, he weighed 6·5 kg., and was 82·4 cm. in height. He was of quick apprehension and good memory, and his intelligence, in spite of the extreme smallness of his head, was excellent. Ranke considered him to have the proportions of an adult, though his head and feet were a little too large, and his arms a little too short.

Nothing was said of the sexual organs, except that they were undeveloped.

It was computed that for seven years he had grown at the rate of 2·7 cm. a year.

CASE 2.—Another example of a similar condition was also examined by Ranke and von Voit.‡ This was that of Millie Edwards, who was of the age of twelve years. She is described as being of a very quick and lively disposition, and of excellent intelligence and memory. She was 72 cm. high, and weighed 6·6 kg., but no other measurements are given, though it is stated that her proportions were correct.

CASE 3.—A still more striking case is that of Pauline Muster, a

* ‘Zeitschrift f. Ethnologie,’ 1883–4, Bd. xv.

† ‘Arch. f. Anthropol. Braunschweig,’ 1885–6, Bd. xvi, S. 228.

‡ *Loc. cit.*

Belgian dwarf, who was no more than 30 cm. in length at birth. She was examined by Virchow* at the age of three years, when she weighed 3.63 kg., was 53.8 cm. high, and measured 36.3 cm. round



FIG. 24.—“General Mite” (1), aged 16 years, standing beside a man of ordinary height. From a photograph by the London Photographic and Stereoscopic Company.

the head. At the age of five she was examined by Dr. A. A. Bouchard,† who found that she was then 55 cm. high, and that the

* ‘Zeitschrift f. Ethnologie,’ Bd. iv, S. 215.

† ‘Journ. d. Méd. de Bordeaux,’ 1884-5, vol. xiv, pp. 276-279.



FIG. 25.—*Dwarfs with microcephalic features*: (2) General Mite. (3) Millie Edwards. (4) Pauline Muster. (5) Lucia Zarate. (6) The Corsican Fairy. Observe in each case the smallness of the head compared with that of the normal man; yet there is no appearance of smallness because the proportions of the body are adjusted to the size of the brain. There is a close resemblance between different dwarfs of this type. The intelligence was good in each case, with the exception of that of Lucia Zarate (5), who was an imbecile. She reminds one of Caroline Crachami (p. 599), and may have been an example of the same disorder. Compare with the ateleiosis group on p. 586. Fig. 5 is from a photograph by the London Stereoscopic and Photographic Company.

circumference of her head had increased to 39 cm. She had twenty-two teeth, but no particulars are given of the state of dentition. Virchow noticed that she talked with quickness and volubility, and was exceedingly bright and lively. She is described by others as being in perpetual movement and of good intelligence.

No examination of the bones was made in any of these cases; we cannot, therefore, say positively to what class of infantilism they belong. It will be noticed that the intelligence was good in all, though the heads were very small. The size of the head and length of the body of Pauline Muster were very near to those of Caroline Crachami, but it should be observed that there was in reality a difference between them, for Caroline Crachami, at the reputed age of nine years, was of about the same size as Pauline Muster at three. They possessed many of the features of microcephaly. Different observers seem to have been much struck with their quick movements and extreme restlessness, and if we compare the facial characters of a group of these dwarfs with those of the case of undoubted microcephalic idiocy described on p. 574, we notice that while the different members of the group bear a striking resemblance one to another, their features also resemble those of the idiot. Though they show no particular enlargement of the nose, their chins are definitely receding. They all die young. Pauline Muster is said to have died from pneumonia in New York. We have a portrait of "General Mite" as he appeared when approaching puberty. His features had become coarser and more definitely of the microcephalic type. He was said to have grown much taller and to have entered an Australian asylum as an imbecile.

Mongolism.

We owe the terms "mongol" and "mongolism" to Dr. Langdon Down, who first applied them to a form of idiocy in which obliquity of the eyes, flatness of the face, and imperfect development of its features are suggestive of the Chinaman.

It is Dr. Shuttleworth's opinion that the mongol idiot represents a permanent defect of development originating in foetal life. He says that some 40 per cent. are the youngest members of large families, and are probably the outcome of depressed procreative power on the part of the mother.* According to Dr. Sutherland, syphilis was present in no less than 44 per cent. of twenty-five cases

* 'Lancet,' 1900, vol. ii, p. 1429.

seen by him, but Dr. Fletcher Beach* believes that it accounts for only 1 per cent. of his cases.

The disease is, therefore, not in reality post-natal in origin, but



FIG. 26.—*Mongolism*: The child is plump, the face flat, and the expression vacuous. The attitude of attention is fallacious. Owing to restlessness and inattention many photographic plates were spoiled before he could be induced to fix his gaze in this manner. Aged 8 years.

is clearly pre-natal. At the same time it is distinctly an infantilism. Those affected are short, have broad, small heads, and short, flat faces, with immature, depressed noses, and features devoid of

* *Ibid.*

character. The contour of the body and limbs is, as a rule, more rounded than usual, even when maturity is reached. Sexual characters are backward in appearing, and are always defective. There is often complete arrest of development of the sexual organs from the beginning, with occasional cryptorchism. The hands are small and short, the anterior fontanelle closes late, but ossification and dentition are delayed, and the teeth are small and widely separated.

The convolutions of the brain are also characterised by defective development. They are less distinct than usual and are broad and flat with shallow sulci. The intelligence is decidedly impaired, though not, as a rule, to the point of idiocy. Mongol imbeciles are generally capable of being taught easy reading and writing, and can be employed in the least difficult forms of manual labour. They are quite unable to calculate, but, as is so often the case in the mentally defective, their musical sense is well developed.* As a rule mongols die young, either from tubercle, pneumonia, or bronchitis, or from gastro-intestinal troubles.

Associations.—Mongol imbecility is peculiarly prone to be associated with pre-natal *heart disease*. Dr. Archibald Garrod has drawn special attention to the fact in the course of a brief description of five cases.† Other pre-natal malformations also occur, such as *spina bifida* and *club-foot*.

Deformity of the little finger is a frequent accompaniment of mongolism, the last phalanx being turned inward. This, as well as a “double-jointed” condition of the thumb and a tendency to knock-knee, probably result from a laxity of the ligaments.

Sexual Infantilism.

Next to the thyroid gland, no organ seems more likely to be the responsible element in infantilism than the sex organs. Their association with immaturity in general is, under normal conditions, so intimate that it might be anticipated that any very striking defect of development would be sure to be correlated with general infantilism in a large proportion of cases.

But in reality this anticipation is hardly verified by facts, the main reason being that when the chief organs of sex are deficient, the secondary manifestations of sex rarely remain neutral, but

* Dr. Comly, ‘Arch. de Méd. des Enfants,’ No. 4, 1906; Dr. Still, ‘King’s College Hospital Reports,’ vol. vi, p. 51.

† ‘Brit. Med. Journ.,’ 1898, vol. ii, p. 1255.

swing over into opposite sex characters. Masculinism or feminism, therefore, is a more common result than infantilism. No doubt arrest of development of the testes or of the ovaries does sometimes precede the ateleiosis by some years; but this priority by no means proves that it is the determining factor.

In all probability, when well-marked ateleiosic infantilism is combined with sexual deficiency, the correlation is of such a nature that the case must be regarded as one in which the ateleiosis is primary however much the local derangement may precede the general in order of time. The reason for this view will appear later on.

At the same time it is conceivable that the general development of a child with defective sex organs might be far more amenable to the influence of the causes of ordinary (minor) infantilism. Indeed, the same deteriorating causes would be calculated to produce the negative state of infantilism rather than the more positive feminism or masculinism.

Infantilism of Indeterminate and Mixed Causes.

Cases of infantilism cannot always be classified. The cause may have ceased when the patient came under observation or it may escape detection, or there may be many different causes.

Infantilism of Combined Lorain's and Brissand's Type due to Mixed Causes.

Drs. Dupré and Pagniez* describe an instance of "Infantilisme dégénératif (type Lorain) compliqué de dysthröide pubérale" (type Brissand) in a youth of fifteen and a half, 1.27 m. high, whose father and mother were both addicted to alcohol. He was a

* 'Nouvelle Iconograph de la Salpêtrière,' t. xv, 1902, p. 124.

premature (eight months) child, and had suffered from whooping-cough, scarlet fever, and (doubtful) enteric fever. The delay of development seems to have started at five as a result of this last illness, and was ushered in with somnolence, impaired appetite, and hysterical crises.

It is highly probable there were many causes, not the least of which was the alcoholism of the parents.

Pancreatic Infantilism.

This form of infantilism was first described by Dr. Byrom Bramwell.* In his case a lad, aged 18 years and 10 months, of good intelligence, had suffered from chronic diarrhoea of nine years' duration, associated with complete arrest of bodily development for the same time. The genitals were infantile, the voice shrill, the pancreatic secretion defective or completely absent. The administration of pancreatic extract for nine months resulted in decrease in the number of motions from four, five, or six a day to two or three, in a gain of $8\frac{1}{2}$ lb (3·85 kg.) in weight, and in a growth of $1\frac{7}{8}$ in. (4·7 cm.) in height. Three years afterwards the gain in weight amounted to $23\frac{3}{4}$ lb. (10·770 kg.), and in height to $5\frac{7}{8}$ in. (14·9 cm.), while there was considerable development of the sex organs, and the voice had become low-toned and rough. The deficiency of pancreatic secretion was proved by an ingenious method suggested and carried out by Dr. Young, by the presence of fatty stools, and by the giving of Prof. Sahlis's test capsules.

It is most unlikely that pancreatic inadequacy in children invariably gives rise to infantilism. For the production of infantilism the cryptic element which constitutes the minor variation is probably essential. Then, of course, there is the *cause*. But by what agency the pancreatic inadequacy is induced does not seem to be determined. Probably the defective secretion acts in more ways than one. In the first place it induces a state of semi-starvation by interfering with the digestion of fats and carbohydrates; in the second place it is possible that there is a toxic element produced in the way suggested by Herter; and in the third place the influence of correlation probably comes in to facilitate the action of starvation and intoxication.

* 'Clinical Studies,' vols. i and ii, 1903-4.

V

GENERAL INFANTILISM OCCURRING AS A MAJOR VARIATION; ESSENTIAL INFANTILISM; ATELEIOSIS

This form of infantilism is characterised by absence of perceptible cause, by the presence of heredity, and by the pronounced degree of the developmental defect. It is of two kinds—sexual and asexual. In some cases of *sexual* ateleiosis the only indications of infantilism are to be found in the size of the body and in the proportions, which are infantile, the primary and secondary sexual characters being of the adult type. In *asexual* ateleiosis the whole body, including the sex organs, is infantile. The asexual is probably nothing more than the sexual form in which the reproductive organs have undergone correlative infantilism. A case is given in which a man with sexual ateleiosis was the father of a son with asexual ateleiosis. *

Introductory.

The Differences Between Ateleiosis and Common Infantilism.

It has been stated in a former chapter (p. 146) that the distinguishing features of a discontinuous variation are its (1) spontaneous appearance, (2) pronounced degree, and (3) hereditary transmission.

All these characters are forthcoming in the form of infantilism about to be discussed.

One of the most remarkable features of this condition is the entire absence of illness among those cases which have come under our notice. In other forms of infantilism the individual affected has shown some sign either of disease or of debility the result of disease, or, at any rate, has dated his arrest of growth from some disorder which has obviously been a striking event in his history. But this is not the case with these ateleiosic dwarfs, all of whom have seemed, except in regard to their infantilism, to have lived ordinary lives, punctuated, it may be, with childish, half-forgotten ailments, but never at a time or to a degree which would lead one to suspect them of being causes of the developmental delay. They seem to occur as sports or “freaks of Nature,” entirely irrespective of circumstances. Moreover, their want of fitness to their circum-

stances and unlikeness to their family is accentuated as they grow older. In ordinary infantilism the affected person retains more or less



FIG. 27.

of the facial appearance and other characters of his parentage, but the ateleiosic individual looks unlike every other member of his family. In all cases he has features which are quite *sui generis*.

Indeed, in typical cases his physiognomy is almost as striking and distinctive as is that of mongolism or cretinism.

A necessary corollary to this characteristic disposition of the features is that the subjects of this form of infantilism closely resemble one another. In fact, they are almost as much alike as cretins. This point is well illustrated by the appended figures, which represent a number of dwarfs of this type. So alike are the subjects

KEY TO FIG. 27.

1 2		3	5	
		4		
6	7	8	20	
9, 10, 11			19	
			18	
12, 13		16	17	
		14	15	

FIG. 28.—Group of dwarfs showing features of ateleiosis. Compare with group of dwarfs with ordinary infantilism (Fig. 22). The features are those of stereotyped childhood. Hence the stature is small, the limbs short, the head large, and the face broad and flat; the bridge of the nose is undeveloped, and the distance from the ear to the vertex is comparatively great. The facial type is so well defined in some cases (Nos. 5, 9, 10, 11, 14, 15, 16) as to obliterate the natural expression of character and produce a strong resemblance between dwarfs of different families. But added to these childish features are the lines and superficial markings of age. In the case of No. 9 there is facial hair, and in at least four others (Nos. 6, 11, 14, 15) there was evidence of sexual maturity. All these dwarfs have been exhibited in variety shows, and are, or were, of good intelligence. The most noteworthy of the group are Charles Stratton (No. 14), who was known as Tom Thumb, and his wife (No. 15) Lavinia Warren. Minnie Warren (No. 11), sister of Lavinia, married George Washington Nott (No. 10), who died in 1881 at the age of 33 years. No. 9 is known as Baron Magri. Bornwalski (No. 6) was born in Poland in 1739, and died at Durham in 1837, aged 98 years. The photograph is from a portrait in oils in the Hunterian Museum of London. No. 3 is the French dwarf described on p. 605; and No. 17 is described on p. 603. Nos. 12, 13, 19, and 20 are the German brothers Franz and Carl Rossow; No. 4 is Annie Nelson, and No. 16 the mulatto known as Chiquita. Figs. 9, 10, 11, 14, 15, are from photographs by the London Stereoscopic and Photographic Company.

of ateleiosis that when a number of them belonging to different families are collected together in a troupe for show purposes they sometimes resemble one another even more closely than do brothers

and sisters. Barnum, in his very candid autobiography, says that during the period of his exhibition of "Tom Thumb," if the latter were not available he would put "Commodore Nutt" in his place, and no one ever detected the deception.

This extraordinary resemblance was noticed by a European traveller who lived in the eighteenth century.* Writing of the court dwarfs of Russia and Poland, after some comments which serve to show that the dwarfs are of the type now under discussion, he says: "It is very curious to observe how nearly they resemble each other; their features are all so alike that you might easily imagine that one pair had spread their progeny over the whole country."

The explanation of this striking facial resemblance is to be found



FIG. 29.—From Lavater's 'Essays on Physiognomy.'

in the fact that the features which characterise the most pronounced form of ateleiosis are those of perpetual babyhood, and just as babies resemble one another much more closely than is the case with adults, so is it with this stereotyped infancy. The features typical of ateleiosis are the relatively large head and the short, broad, flat face, usually significant of the infantile period of life, before the increase in size of the nose and of the upper jaw have lengthened the physiognomy and enlarged and diversified its characters.

Lavater† showed the acuteness of his observing faculties in his remarks on a female dwarf (Fig. 29) who came under his notice. He alludes to her as follows:

"I subjoin the profile of a girl of sixteen, whose stature scarcely exceeded two feet. Her physiognomy suggests absolutely no other idea but that of a *consolidated infancy*. The forehead bent forward indicates the physical imperfections of the first stage of human life,

* Porter, 'Travels in Russia and Sweden.'

† 'Essays on Physiognomy,' translated by Moore, vol. iv, 1797, p. 160.

and the hollow inflections of the root of the nose is the infallible sign of mental weakness, or want of vigour. . . .

“This dwarf, however, did not want sense, or rather, she could prattle, and had a retentive memory.”

The facial appearance is not the only peculiarity of ateleiosis. Of equal importance in serving to distinguish it from secondary infantilism is the retention of infantile size and proportions of the body and limbs. So small are these dwarfs that they are especially selected to be served up for the satisfaction of the public curiosity in variety shows.

And it is not only in regard to size that ateleiosis shows its peculiarity, but also in respect to proportions. The limbs are usually very short, and the proximal segment (humerus or femur) may be short when compared with the distal. Owing to the shortness of the lower limbs and the relative bigness of the head, the middle point of the body, instead of being at the pubic symphysis, as in normal adults, is nearer the navel, where it is in infancy.

In all these respects this form of infantilism differs from the ordinary form. Only one other character need be alluded to, and it is one of the most important of all. This is the fact of heredity. The heredity may be either direct, so that the condition is transmitted from parent to offspring, or it may be familial, two or more of the children being affected, while the parents are normal. In one of our cases the infantilism was transmitted through at least three generations, implicating four individuals, but as a rule the heredity is familial.

Local Irregularities of Growth or Development in Ateleiosis.

One of the features of infantilism in general, both primary and secondary, is the irregularity of its manifestation. This is especially true of common infantilism, in which the development of one part of the body may be much behind that of other parts. We have seen that this statement applies more particularly to the nervous, cardio-vascular, thyroid, and sexual system, though it is probably more often noticed in these organs chiefly because the effects produced are of such a nature as to enforce attention.

Much the same might be said, though with less certainty, of ateleiosis. In this condition also certain organs are prone to lag behind in their development to a greater degree than others. On a first study of this disorder one is deceived into thinking that in this fact is to be traced the clue to the origin of ateleiosis. Indeed,

what can seem more likely than that the local impairment of function of the thyroid gland, the hypoplasia of the pituitary body, or of the arterial system, or of the sex organs, which so often occurs in ateleiosis to a more obvious degree and prior to the general infantilism, is causal in nature?

But fuller investigation tends to erase this impression, and to replace it with the conviction that they are secondary phenomena, the expression of the fact that one has to do with a variation, and a variation so extreme that it is pathological, and is therefore correlated with other pathological variations. Moreover, we have seen (p. 97) that of these associated variations those of the sex organs are among the most common, so that the perpetuation of the undesirable variation tends to be automatically stopped by means of sterility. This fact is of such consequence in its bearing on ateleiosis as practically to give rise to two varieties.

The Two Varieties of Ateleiosis.

In one of these varieties there is conspicuous delay of both growth and development up to the onset of puberty, which may itself be delayed. The sexual system then matures, fusion of the epiphyses takes place, and the growth of the body becomes arrested, leaving the individual sexually complete, but in other respects with the proportions and outward appearance of stereotyped childhood. This may be termed the "sexual variety."

In the second, or asexual, variety there is conspicuous infantilism throughout the whole of life, for the sexual system never matures, and growth slowly continues up to the age of thirty, or even later.

It is not to be expected that every case of ateleiosis will present unmistakable evidences of its nature. On the contrary, it may be conjectured that while most instances of this affection will conform pretty closely to pattern, some will be met with of which it is not so easy to say off-hand whether they are or are not examples of this form of infantilism. Exactly the same may, indeed, be said of cretinism, of achondroplasia, of cancer, and, indeed, of any other disease. But for the purposes of demonstration it is obviously best to select strongly marked examples to serve as types. In the case of the sexual variety of primary infantilism none can better serve our purpose than the well-known Americans, "Tom Thumb" and his wife.

VI

SEXUAL ATELEIOSIS

Charles Stratton (Fig. 30), afterwards known as "Tom Thumb," was born at Bridgeport, U.S.A., in January, 1832. At birth he is said to have weighed 9 lb. 2 oz. (4.566 kg.). At the age of five months, when he ceased to grow, he weighed 15 lb. (6.802 kg.), and measured 23 in. (0.552 m.) in height.

In January, 1844, when fourteen years old, he was brought to Great Britain by Barnum, and the next year crossed into France. It was then noticed in the public prints that his voice was still of a childish treble, his head large in comparison with his body, hair light and fine in texture, eyes dark, prominent, nose small, upturned, hands and feet little and delicate. His intelligence was good, his behaviour simple, naïve, original, vivacious, and his movements light, graceful, and nimble. In regard to his dentition, Dr. N. W. Kingsley * says: "I examined a few years since the mouth of the celebrated dwarf, Tom Thumb. I found the teeth of a man in individual size, but the maxillæ, in harmony with the rest of his osseous system, were dwarfed. The result was what we should naturally suspect, a most marked malposition of the teeth, so much so that he said 'he had a double row of teeth all round,' and this is uniformly the case with dwarfs where the whole physique is symmetrically dwarfed. The converse is also true of giants, except in those cases where the extraordinary stature is characteristic of race."

In 1863, when thirty-one years of age, he married *Lavinia Warren*, and the next year came to England with his wife, her sister Minnie, and "Commodore Nutt," all dwarfs of the same type. Their marriage is said to have resulted in the birth of a female child of ordinary size, who died from inflammation of the brain in the same year. Though we can find no satisfactory confirmation of this birth, it is alluded to in contemporary prints, and the medical journals of the time refer to it as to an accepted fact.†

* 'A Treatise on Oral Deformities,' p. 8.

† *E. g.* 'The Hospital Gazette of New York,' 1878, vol. iv, p. 81.



FIG. 30.—“General and Mrs. Tom Thumb.” The faces and general proportions show stereotyped infantile characters. Note the shortness of the extremities and the smallness of the hands and feet. \times marks 25 in. (From a photograph by the London Stereoscopic and Photographic Company, Limited.)

[Since this last paragraph was written we have been able to speak to the mother, who is an intelligent, dignified little lady, whose word cannot be doubted. She assures us that the accounts of the birth and death of her son are correct.]

Charles Stratton died in 1883 when fifty-three years of age.

The portraits of Tom Thumb and his wife show a remarkable resemblance in height, build, facial appearance, and bodily proportion. Both are of childish conformation, their limbs being short, heads big in comparison with their bodies, and hands and feet remarkably small. Both have little, undeveloped, turned-up noses, but this peculiarity is especially noticeable in Charles Stratton's portrait, partly because his nose was actually more snubbed, but chiefly because the nose of the adult male is naturally more prominent than the nose of the female, and any defect of this feature is therefore so much the more conspicuous in the male sex.

There seems no reason to doubt that Mrs. Stratton did in reality bear a child, for her configuration, though in some respects childish, in others is decidedly womanly. We ourselves saw her some twelve years ago, and noticed that the breasts and pelvis were so well developed in comparison with her size as to leave no room for doubt that her proportions were conspicuously feminine. We saw her again last year, when she was being exhibited in London together with a large number of other dwarfs, most of them the subjects of ateleiosis.*

Another dwarf of the same type, quite as celebrated in the eighteenth century as was Charles Stratton in the nineteenth, was the Pole, *Joseph Bornwlaski* (p. 586, Fig. 6), born in 1739. Though his parents were of medium size, out of their family of six children three sons are said to have exceeded the ordinary stature, while two sons and one daughter, though they reached adult age, did not attain the height usual at the age of four years.

There are many allusions to Bornwlaski in the writings of his day. In 1760, when he was twenty-one years old, a Count Tressan sent his history and description to the Royal Academy of Sciences of Paris. In 1788 Bornwlaski published an autobiography, with a portrait of himself, his wife, and child.† Though there are a few unimportant discrepancies in these various accounts, they agree in

* See 'Brit. Med. Journ.,' 1909, vol. ii, p. 1768.

† 'Memoirs of Count Bornwlaski.' A copy of this has lately been published by Mr. H. R. Heatley, under the title, 'The Life and Love Letters of a Dwarf.' It contains three good portraits and many interesting comments, biographical and otherwise. Also 'Giants and Dwarfs,' by E. J. Wood, p. 333.

essentials, and there is no reason to doubt the truth of his statements of facts.

He was said to be amiable, cheerful, entertaining, well-informed, and was evidently a man of exceptional ability and simplicity of character. He states in his autobiography that he did not cease to grow until he had attained thirty, his height at different ages being as follows :

		French.	English.	cm.
At 3 years	. .	1 ft. 2 in. .	1 ft. 3 in. .	38·5
„ 6	„ . .	1 ft. 5 in. .	1 ft. 6 $\frac{3}{8}$ in. .	46·75
„ 10	„ . .	1 ft. 9 in. .	1 ft. 10 $\frac{3}{4}$ in. .	57·75
„ 15	„ . .	2 ft. 1 in. .	2 ft. 3 in. .	68·75
„ 20	„ . .	2 ft. 4 in. .	2 ft. 6 $\frac{1}{4}$ in. .	77
„ 23	„ . .	2 ft. 11 in. .	3 ft. 2 in. .	96·25
„ 30	„ . .	3 ft. 3 in. .	3 ft. 6 $\frac{1}{4}$ in. .	107·25

According to Boruwlaski his dwarf brother also grew until he was thirty. Boruwlaski married a lady of normal size, by whom he had two children of ordinary stature. At least five portraits of him are extant, one of which is now in the Museum of the Royal College of Surgeons of London. He died at Durham in 1837 at the age of ninety-eight.

Lockhart, in his 'Life of Sir Walter Scott,' appends a foot-note to a reference to Boruwlaski in one of Scott's letters (written in 1814), as follows :

“ Count Boruwlaski was a Polish dwarf, who, after realising some money as an itinerant object of exhibition, settled, married, and died (September 5th, 1837) at Durham. He was a well-bred creature, and much noticed by the clergy and other gentry of that city. Indeed, even when travelling the country as a show, he had always maintained a sort of dignity. I remember him as going from house to house, when I was a child, in a sedan chair, with a servant in livery following him, who took the fees, M. le Comte himself (dressed in a scarlet coat and bag wig) being ushered into the room like an ordinary visitor.”

Though the proportions and physiognomy of Boruwlaski, as shown in his portraits, are not so characteristic as in the two cases we have chosen for a type, they are sufficiently so to be unmistakable. The childish figure, prominent eyes, comparatively large head, and short limbs, with tiny hands and feet, are all present. Perhaps the most interesting character is the delayed growth, probably due to retarded sex development. This is often a feature of this form of infantilism, and seems to connect sexual ateliosis with the asexual variety, to be described presently. Boruwlaski's statements in regard to his

growth and delayed maturity are always consistent. There is evidence that puberty did not begin until about twenty-five. He is not very explicit in his references to the time of his first perceptions of sex, but says, "at the age of twenty-five I was like other young lads at fifteen." He was ardent in his love affairs, and married at forty. Yet two years afterwards he was still a child in appearance, for many ludicrous mistakes were made in this respect. He refers especially to one by his wife's doctor, a physician of some repute, who attended her during her first pregnancy, and for a time could not be made to understand that the little fellow at the bedside was not a child.

There is a remarkable difference between the physiognomy of Bornwlaski as represented in his earlier English portraits and in his later. In the earlier the nose and other features are quite childish. In the later they have become prominent and mature. He evidently came to maturity in some respects but not in all.

One of the most unexpected instances of ateleiosis has been described by De Quatrefages* under the title "*Sur Balthazar Zimmermann, dit le Prince Balthazar, véritable nain microcéphale.*" This title is very misleading, for after describing his dwarf, he compares him with the microcephalic Bébé (see p. 637), and shows that Zimmermann was *not* microcephalic, seeing that his head did not correspond with the head of microcephalics either in shape or in size, while his intellectual faculties were of good development.

Zimmermann was a show dwarf, born in Switzerland, one of a family of which the parents and brothers and sisters, eight in number, were of ordinary size. He was said to have been of normal proportions at birth, his growth being arrested later on. His age was stated to be sixteen, his height 76 cm., and weight 9 kilos, but these measurements were not verified by De Quatrefages. The head was large in proportion to the body, it being one fifth of the total height instead of the normal one-seventh. He was described as having a large forehead, prominent temples, well-marked parietal bosses, and as being brachycephalic. His head "resembled a hydrocephalic head." The cheeks were full, eyes large, mouth small, nose small and undeveloped, it being stunted and narrow at the root, but a little widened out at the nostril. Curiously enough after describing these manifestly childish features, the writer goes on to say that this dwarf had nothing of the figure of a child, but that his physiognomy was "*vieilloté.*" He was serious and a little morose in aspect, and his movements were slow, but he was said to be

* '*Bull. Soc. Anthropologie de Paris,*' vol. iv, sér. 3, 1881, p. 702.

amiable and even gay among his friends. He was of good intelligence and could speak two languages beside his own. His voice was "grêle" and "félée"—high-pitched and piping.

We have ourselves examined a few cases of this form of ateleiosis, two of them being members of the same family, one the father of a boy affected with asexual ateleiosis.

*Two of the Sexual and One of the Asexual Variety.**

CASES 1, 2, 3.—These three cases are of exceptional interest. There is in the first place a strongly hereditary element. The grandfather was a well-known show dwarf, who married a woman of ordinary stature. His brother was tall and was a member of the police force. This dwarf, who is said to have been 47 in. (120 cm.) high, had two children, both of whom are sexual ateleiosic dwarfs and represent two of the cases now being referred to. We have examined and measured both of them. One is a lively woman of good intelligence, 129·5 cm. high, of normal sexual condition, the mistress of a country post and telegraph office. The other, aged 36 years, is a boot rivetter. He states that he almost stopped growing when about one year old, but thinks he grew more quickly at fourteen or fifteen, and ceased altogether at seventeen or eighteen, after the onset of puberty. He married at twenty-five and has had seven children, four of whom died when about three months old. All four are said to have been dwarfs, but of this we cannot be positive. Of the three now living the first is the case of infantilism about to be described; the second and third are well-developed girls. It will be noticed that both this man and his sister are examples of sexual ateleiosis. He is of fair muscular development, and ossification is completed.

But his dwarf son, aged 10 years, is a conspicuous example of the asexual variety. The proportions of the body are those of a child of four; the teeth are of the first dentition except the two central lower incisors, which are just showing through the gum. He is cryptorchid, and his ossification resembles that which is usual at five.

* 'Brit. Med. Journ.,' 1904, vol. ii, p. 914.



FIG. 31.— Cases 2 and 3. On the left is a man of ordinary stature, next to him Case 2, aged 38 years (photograph taken two years after the account was written), then his son (Case 3), aged 12 years, and on his left his normal sister, aged 8 years.

VII

ASEXUAL ATELEIOSIS

Ateleiosis may begin at any age of progressive development. Hence, there seem to be three well-marked varieties—to wit, foetal, infantile, and juvenile. The first is characterised by imbecility, the second and third by the facial and other structural characters of infancy and youth respectively.

Both kinds of ateleiosis are irregular in their manifestations, and seldom occur in typical forms. Some organs are prone to be more affected than others. These organs are chiefly the sexual, thyroid, pituitary, cerebral, and cardio-vascular. There is reason to believe that these are often affected secondarily, by correlation, and are seldom, if ever, the prime factors in the situation.

Ateleiosis is probably an imperfect reproduction of a condition normal at a prior stage of evolution.

THERE is no reason to suppose that the abrupt and spontaneous interference with progressive development which constitutes ateleiosis invariably takes place at one time of life. On the contrary it is highly probable that the time of onset is variable, as is the case with similar defects of organs. We have seen that the early period of progressive development is distinguished by the rapidity of its transitions, so that the foetus, within the space of a few months, is rushed through a series of transformations which in the slow process of evolution probably took hundreds of thousands of years to accomplish. Moreover, this recapitulation does not cease at birth, but continues through the stages of infancy and childhood up to maturity, and during the whole of this period the process of development is liable to be stayed or to be unduly accelerated.

Hence, it is possible for ateleiosis to appear at any age of progressive development, and we seem to be able to detect at least three varieties :

(1) Ateleiosis beginning in foetal life, distinguished by a very remarkable combination of dwarfism with feebleness and imbecility, such as might be expected of a sudden interference with the processes of development at this early age.

(2) In the second group ateleiosis begins during infancy. It is then stamped with the facial and other features which distinguish this time of life.

(3) In the third group ateleiosis begins at some later period of development, and the characters of the disease are more indefinite. They consist in a prolongation or perpetuation of the height and other features of the period of childhood or youth.

Group I. Ateleiosis beginning during Fœtal Life.*

CASE 4.—A skeleton of what appears to be an example of the first or fœtal type is to be found in the museum of the Royal College of Surgeons of England; a portrait of the living original hangs upon one of the walls in the corridor, and a short account of



FIG. 32.—Caroline Crachami. From a painting in the Museum of the Royal College of Surgeons of England. The ateleiosis began in fœtal life. The portraits show the prominent nose and receding chin, characteristic of microcephaly. Compare with figure of Lucia Zarate on p. 579.

her history and her *post-mortem* condition is to be found in the library.

Briefly, the main feature of this case of Caroline Crachami is the extreme delay of general development. In size the skeleton was equal to that of a nearly mature fœtus, the ossification resembled that of most children of little over a year old, the dentition corresponded with that of a child of two, but in no respect was she so backward as in the development of the sex organs. These, according to Sir Everard Home,† who said he examined them after death, were as immature as those of a fœtus of three or four months.

* This account of asexual ateleiosis is for the most part an abstract of articles which have appeared in the 'Med.-Chir. Trans.,' vol. lxxxv, 1902, p. 305, the 'Practitioner,' vol. lxx, 1903, p. 797, and the 'Brit. Med. Journ.,' 1904, vol. ii, p. 914

† 'Lectures on Comparative Anatomy,' vol. v, 1828, p. 191.

As for the intelligence, that seemed to be commensurate with the size of the skull, which was that of a new-born baby. The result was that



FIG. 33.—*Ateleiosis*. Group I. Case 4. Skeleton of Caroline Crachami, aged 9 years (A), standing by the side of the normal skeleton of a child of 15 months (B). The ossification of the former is less advanced than it is in the latter. The skeleton, which is in the Royal College of Surgeons' Museum in London, is distorted by the passage of an iron rod through its cerebro-spinal axis. It is 50.5 cm. in height, but this height is no doubt partly due to the method of mounting.

the child was an imbecile, and though of fairly just proportions, had the facial characters and intelligence of microcephalic imbecility.

At the same time there is no reason to believe that the size of the brain was the dominant factor, but on the contrary, that it was no more than part of the widespread developmental defect.

A case, remarkably like that just described, was published by Beclard * in 1817. This case was also that of a female who died at the same age (seven), and was said to be of the height of the normal infant of one month. Anna Barbara Schreyer, the offspring of a father of ordinary size, had three sisters and one brother all of normal stature. She was born at term, and was in length equal to that of a foetus of four months, and of a weight usual to the foetus of six and a half months. The height at death was 62 cm. (C. Crachami 49 cm.), and her weight 3.854 kg. Her teeth are said to have been like those usual at seven years—in other words they corresponded with her age. Her muscles were well-formed, but subcutaneous fat was almost absent. It is evident that she was very restless, for it was said to be impossible to count the pulse, owing to her incessant movements. Nothing is said about her mental condition.

Group II.—Ateleiosis beginning during Infancy or Early Childhood.

It is in this group that ateleiosis presents itself in the most characteristic form. In all probability the first case to be described was that brought forward by *Prof. Schaaffhausen* in 1868.† This was a male, aged 61 years, who was 94 cm. in height, and the circumference of his head 20 cm. There were three other instances of a similar condition among his brothers and sisters. He was of average intelligence, showed characteristic childish conformation of face and cranium, and was a double cryptorchid. He died from cerebral hæmorrhage. After death stenosis of the aorta and pulmonary arteries was found, together with atheroma of the semilunar valves and basilar arteries. Fourteen years afterwards‡ *Schaaffhausen* obtained the skeleton and found that nearly all the epiphyses were still ununited.

By far the most complete description of the disorder is that

* 'Bull. Faculté de Méd.,' Paris, 1817, p. 486, "Notes sur une naine de l'âge de sept ans ayant à peu près les proportions d'un enfant naissant." See also 'Histoire des Anomalies,' by St. Hilaire; 'Les Nains et les Géants,' by Garnier, p. 61, where evidently the same child is described under the name of "Babet Schreier."

† 'Verhandl. d. Naturhist. Vereins d. preuss. Rheinl. u. Westphal.,' 38 Jahrg., Erstes Heft, Bonn, 1868, S. 26.

‡ *Ibid.*, 39 Jahrg., S. 10.

given by *Dr. Arnold Paltauf** in 1891. His patient was a male, aged 49 years at death. He was 122·5 cm. high, and his head was 54 cm. in circumference. He was of good intelligence. The genital organs were infantile. He died from tubercular disease of the lungs. The thyroid gland was found to be small and pale, but its weight is not given. The sella turcica was abnormally large, it being 6 mm. longer and 3 mm. broader than is usual in adults. Ossification was no further advanced than that which is commonly met with in boys of seven years of age. A microscopical examination of some of the epiphysial cartilages showed appearances resembling those which characterise normal ossification, combined with the calcification-changes which are associated with old age.

Dr. Manouvrier† patient was a male, aged 23 years, 17 kgrm. in weight and 99 cm. high, the head measuring 539 mm. in circumference. He was normal at birth. He fell downstairs at three years of age, but impairment of growth was not noticed until he was four. Growth to the extent of 4 cm. took place between seventeen and twenty-one. Some of the milk-teeth were still persisting. The genital organs were infantile, and the facial appearance, proportions and gait were childish. A portrait which is reproduced with the article shows that he possessed the flat, broad face and *retroussé* nose characteristic of ateleiosis.

Dr. Joachimsthal,‡ of Berlin, gives an account of a troupe of dwarfs. Four of these appear to have been instances of the asexual form of ateleiosis. The disorder was first noticed in the third, seventh, eighth, and tenth years respectively; and though the ages varied from thirty to thirty-six years, there was evidence in each case that recent growth had taken place. The tallest of them was no higher than a normal child of eleven years.

Personal Cases.

CASE 5.—Of our own cases published in the 'Transactions' of the Royal Medical and Chirurgical Society of London in 1903, the first, that of a male, aged 28 years, was first noticed to be abnormal when between one and two years old. No cause could be found, and no other members of the family were affected. We examined him at intervals between the ages of twenty-three and twenty-eight, during which time he increased in height from 1·078 m. to 1·096 m.,

* 'Ueber den Zwergwuchs in Anatomischer und Gerichtsärztlicher Beziehung,' 1891.

† 'Bull. Soc. Anthropol.,' 4^e série, tome vii, 1896, pp. 264-290.

‡ 'Deutsch. med. Wochenschr.,' Bd. xvii, 1899, S. 269.

a growth of 18 mm.* He was of good general health and was intelligent.

The dentition was backward, the teeth being partly of the temporary and partly of the permanent set. He was markedly



FIG. 34.—*Ateleiosis. Group II. Case 5.* T. L. S—, aged 28 years, height 3 ft. 7 in. (1'096 m.), standing between a normal adult man and a normal boy of 6 years. The physiognomy and proportions are childish, and the sexual organs infantile, while the attitude, expression, and the markings of the face are suggestive of a more advanced time of life.

childish in conformation, his height being that of a boy of between six and seven, his head big (49·5 cm. round), limbs short, face broad, and the bridge of the nose sunken. His contours also were eminently childish, and his voice was treble.

* Dr. Batty Shaw ("A Clinical Lecture on Ateleiosis," in the 'Clinical Journal,' vol. xxxvii, 1910, p. 136), who examined this dwarf in 1910 (aged 36 years), found that he had grown to a height of 1'138 m. In thirty-five years of his life he had grown as much as most children grow in five years.



FIG. 35.—*Ateleiosis. Group II. Case 5.* Radiogram of hand of Fig. 34, aged 28 years. The ossification resembles that which is usual at from ten to twelve years. Note the size of the hand.

The testes were undescended, and his whole sexual system was infantile. The ossification corresponded with that of most boys of about ten years old. At the same time the wrinkling of the face and the texture of the skin were more nearly in keeping with his age.

CASE 6.—The next case was that of a French girl, aged 18 years,



FIG. 36.—*Ateleiosis. Group II. Case 6.* Aged 18 years; height 1.850 m. A normal adult hand is introduced for the sake of comparison. Note the characteristic physiognomy and the crowded teeth. A radiogram showed that ossification was equal to that which is usual at six years.

whose stature, dentition, rate of growth, intelligence, and sexual condition were much on a par with those of the preceding case. Her height was 1.850 m., the circumference of the head 445 mm. The ossification resembled that usual at six years. She seemed normal in every other particular, and nothing in her past history or that of her family threw any light on the origin of the ateleiosis.

CASE 7.—We also found evidences of ateleiosis in a skeleton in the

Barclay Collection of the Royal College of Surgeons of Edinburgh. This was described as the "skeleton of the dwarf, Bobbie Fenwick, who died in 1815, upwards of fifty."

The skeleton was found to measure 1.188 m. in height, but allowance must be made for a too liberal use of intervertebral cement. The skull measured 505 mm. in circumference. All the bones were lightly formed, and the prominences for the attachment of muscles were inconspicuous, but what was most remarkable was that many of the epiphyses were still ununited. The dentition also more nearly resembled that of a child or youth than of a man of fifty.

CASE 8.—E. G—(Figs. 39, 40, 41), aged 12 years, was the only abnormal member of a family of eight. He almost stopped growing when about two years of age though in good health at the time. The mother says he has grown a little since he was three years old, and that he now wears the same sized clothes that he wore at seven.

He is of good intelligence, with a broad, flat face, *retroussé* nose, and thin lips. The head is flattened on the top and the hair encroaches on the forehead, reaching halfway down the temples. The whole configuration is that of early childhood. There is no sign of cretinism or of rickets. His epiphysial ossification is about one year behind that of his brother of six; dentition is backward and the teeth are crowded. He is a double cryptorchid.

A case of well-marked ateleiosis has recently been recorded by Dr. Parkes Weber* together with two good portraits. He was aged 42 years, had the physical development of nine or ten, was of the height of a boy of eight, but showed the wrinkling of age, and was pre-natal in his sex development.

The skiagram of the hands shows a deep shadow bordering those epiphyses which are not yet joined. The colour of the face, the fineness of the hair and the size of the thyroid gland suggested an element of myxœdema, but in the words of Dr. Weber "these features may be merely a part of the general infantilism."

We have ourselves examined or inspected more than twenty examples of this form of ateleiosis. This is no occasion to enter into detailed particulars, seeing that some good examples of these cases have already been published. All were distinguished by extreme delay of general development. All were intelligent, some after a simple childish fashion, others giving indications of a more mature or adult order of mind. The bodily configuration and facial characters

* 'Proc. Roy. Soc. Med.,' Clinical Sect., June, 1910, p. 143.



FIG. 37.—*Ateleiosis*. Group II. Case 7. Aged 50 years; height, 3 ft. 10 in. (1.188 m.). Skeleton of Bobbie Fenwick, from the Royal College of Surgeons' Museum, of Edinburgh. The bones are delicately formed, the epiphyses about the knee-joint are relatively large, and many of the epiphyses are not united. The spine is too long and the thorax distorted, owing to the insertion of an excess of inter-vertebral cement.

were, in most cases, pre-eminently childish, and when X-ray photographs were taken the ossification was invariably found to be also of childish type and a little in advance of the general development. The dentition was, as a rule, very backward, in some cases to such a degree that many of the milk teeth were retained into the third or even fourth decade, and the jaws were crowded with half-erupted permanent teeth mingled with more or less decayed temporary teeth.

But of all the organs the sexual seemed to be most backward, and the secondary indications of sex were correspondingly in abeyance. Nevertheless it could not be said that in any case were there opposite sex characters, the state being invariably one of infantilism and not of feminism nor masculinism.

It is not possible with our present imperfect knowledge to draw a sharp line between sexual and asexual ateleiosis, for though in some cases cryptorchism or some equivalent defect of ovarian development puts the question of sex influence out of court, in other cases there is reason to believe that the sex organs merely remain dormant for an unusually long time. At any rate, in some instances (*c. g.* Boruwlaski) there is apparently a very long period of sex neutrality and of extremely delayed growth, but this state is not final, for at last sex instinct appears, and with it evidences of sexual maturity, so that the case, which seemed at first to be asexual, eventually turns out to be of the sexual variety.

In referring to some well-known historical instances of sexual ateleiosis, mention was made of the fact that Boruwlaski, though a virile dwarf, did not cease growing taller until he had attained his thirtieth year. There is another example of a dwarf who was also said to have continued growing long after he had attained years of discretion, but in whose case there is reason to believe that he was not sexually mature.

This was *Jeffrey Hudson* (Fig. 38), born at Oakham in 1619. Fuller said that his father was a "very proper man, broad-shouldered and chested, though his son never arrived at a full ell (45 in.: 114·5 cm.) in stature." His mother and brothers also were of full size. "When he was between seven and nine years of age, without any deformity, wholly proportionable, and scarce a foot and a half in height," as described to Fuller by an eye-witness, he was presented to the Duchess of Buckingham. He was afterwards brought to the notice of Charles I, and became a court dwarf. According to his own statement he remained of the height of 18 in. (45·7 cm.) from the age of eight until the age of thirty years, after which

period he increased to 3 ft. 9 in. (114.3 cm.) in stature, and so remained. (Compare with measurements on p. 610.)

Though treated with scant ceremony, and the victim of many practical jokes, he was possessed of uncommon intelligence, and was at one time employed in some important diplomatic missions. He fought a duel in 1653, killing his antagonist, and himself died in 1682, at the age of sixty-two.

There are many of his portraits extant, and all show him to have been of the same type as Charles Stratton. In the full figure in oil by Mytens, now in the National Portrait Gallery, he is represented as symmetrically formed after a childish pattern, his limbs, the upper especially, being short; the forearms and legs, moreover, are remarkably short as severally compared with the arms and thighs, the hands and feet small and delicate, the head large, the nose *retroussé*, and the eyes full. No facial hair is shown, though the fashion then was to wear a peaked beard, and not a word is said in the many accounts of his life of any leanings towards feminine society. Such facts as these, combined with the delayed ossification, suggest that Sir Jeffrey Hindson was an ateleiosic dwarf of the asexual kind.

In addition to these cases there are others which have been referred to by Neumann,* Professor Quetelet,† Sir G. M. Humphry,‡ Dr. N. W. Kingsley,§ Messrs. Gould and Pyle,|| Dr. W. H. Weir.¶ Some information may also be gathered from the Natural History of Geoffrey St. Hilaire,** and from certain semi-scientific authors, such as E. Garnier,†† Le Ronx and J. Garnier,‡‡ and A. J. Wood,§§ and from the very candid account by Barnum.||||

Group III.—Ateliosis beginning between Childhood and Puberty.

We have seen one example (Fig. 42, p. 620) of infantilism possessing the characters of ateliosis of this group.

CASE 9.—In this case a boy (Fig. 42), whose parents and six

* 'Wochenschr. d. Gesell. f. Heilkunde,' Berlin, 1842, S. 705.

† 'Anthropométrie.'

‡ 'On the Skeleton.'

§ 'Oral Deformities.'

¶ 'Anomalies and Curiosities of Medicine.'

• 'Journ. of Path. and Bact.,' vol. viii, 1902.

** 'Histoire Naturelle.'

†† 'Les Nains et les Géants.'

‡‡ 'Acrobats and Mountebanks.'

§§ 'Giants and Dwarfs.'

|||| 'Life of P. T. Barnum.'



FIG. 38.—JEFFREY HUDSON. Aged about 18 years. From a Dutch portrait now in the National Portrait Gallery. Compare with portrait of Boruwlaski on p. 586 (No. 6).

A writer in the 'Times' of January 10th, 1911, estimates from the measurements of Hudson in his portraits that he was 2 ft. 4 in. (71 cm.) at 8; 2 ft. 10 in. (86 cm.) at 11; 3 ft. 2 in. (96.5 cm.) at 18; and 3 ft. 5 in. (104 cm.) at 21.

brothers and sisters were of ordinary stature, seemed from no perceptible cause to stop growing at the age of thirteen.

When we saw him he was twenty-eight years old and of the height, proportions and skeletal development of a boy of fourteen. He had sufficient intelligence to carry him through the fourth standard at school, but was too small and too stupid to be able to earn more than 3s. 6d. a week in minding sheep on a farm.

He died at the age of twenty-eight from influenza and pneumonia. At the *post-mortem* examination most of the organs were found to be of a size corresponding with the size of the body. The mitral valves were crumpled and thickened with atheroma, but did not seem to be incompetent, and there was a well-marked but not patent ductus arteriosus. The testicles together weighed 1 gm. One was undescended and the other was of childish or even infantile development, but was not otherwise abnormal.*

* For further particulars see 'Med.-Chir. Trans.,' vol. lxxxv, 1902, p. 305.

VIII

THE PATHOLOGY OF ATELEIOSIS

AMONG the few cases of ateleiosis hitherto described certain organs have been found in such a state of defect or of degeneration as to be open to the suspicion of being the cause of the infantilism.

These organs are the (1) sexual, (2) thyroid, (3) pituitary, (4) cerebral, (5) cardio-vascular.

(1) Nothing at first seems more likely than that the asexual form of ateleiosis is no more than a form of infantilism secondary to the defective development of the *sexual organs*, especially as in all the cases reported the sexual defect seems to have come first in order of precedence.

On the other hand some would regard it as of thyroid origin, and term it "*myxœdema frustré*," that is, a form of mild myxœdema in which the defects of general development and of the sexual organs are far more pronounced than other symptoms of athyroidism.

But one cannot accept either of these views without doing a certain amount of violence to clinical principles. To say that the sexual defect is the cause is to account for individual cases at the expense of general experience, for it is well known that, generally speaking, hypoplasia of the sexual organs is associated with an adult development. Moreover, there is apparently no case on record of their removal in childhood being followed by infantilism, but by masculinism or feminism.

(2) Much the same applies to the *thyroid* hypothesis of asexual ateleiosis. Hypoplasia, or removal of the thyroid gland, does not lead to mere infantilism, but to cretinism or myxœdema or their equivalents, and it is not easy to accept the opinion that two symptoms of cretinism—general delay of development and sexual hypoplasia—may occur in an extreme form, while other and equally characteristic symptoms are conspicuously absent. Thus in our typical case (p. 602) the general infantilism was so extraordinary that

up to the age of twenty-eight years this "man" looked (at a distance) like a little boy, and was in the habit of travelling on the railway with a half-ticket. In passing through London he could not get cabmen to take notice of his shrill cries of "Hansom" until he had first explained the situation to a policeman.

Yet his intelligence was unusually good, and there was not the slightest sign of that leisurely speech, coarseness of feature, dryness of skin, slowness of pulse, and susceptibility to cold which hitherto have been regarded as cardinal symptoms of myxœdema. Though simple in his ways, like a child, he was of quick intelligence, and fully alive to his position. He readily adapted himself to changing circumstances, and kept pace with his school-fellows in their lessons without any difficulty. To term him an example of cretinism or of myxœdema is to deprive the word of all meaning.

(3, 4, 5) Objections of the same nature may be brought against the view that ateleiosis, sexual or asexual, is due to impairment of the *pituitary body*, or of the *cerebral* or *cardio-vascular* system. The very diversity of these local changes tends to rob them of any such significance. Just as we say of the treatment of whooping-cough, of warts, or of ringworm, that the multiplicity of drugs advocated as cures must be regarded as proof that there is no cure, so the very number of organs affected in different cases of ateleiosis is *primâ facie* evidence that none of them is solely responsible for the infantilism.

It seems far more likely that the disproportionate infantilism or degeneration of the sexual apparatus, of the thyroid gland, or other organ, is merely an associated affection, and does not act as a cause. The most reasonable view to take is apparently to regard local and general infantilisms as a conjunction of two distinct but associated conditions, of the same nature as those similar associations we have noticed in the chapters on the defects of development and degeneration of organs. Just as degeneration of the red-blood system (pernicious anæmia) is prone to be combined with degeneration of the spinal cord, and defective development of the brain with a similar affection of the supra-renal capsules or of the spinal canal, so also it can be understood that defective development of the whole body may very well be accompanied by infantile development of the thyroid, or of reproductive glands, without the one being necessarily the direct consequence of the other.

We regard ateleiosis as an essential defect of progressive development of the whole body. It may be associated with a similar defect, or with premature degeneration, of some particular organs

and, if the sexual organs happen to be the part implicated, the result is the asexual variety.



FIG. 39.—E. G — (on the left), aged 12 years, standing beside his normal brother of 6 years. Except for the texture of his face, E. G — looks the more juvenile of the two. His physiognomy, proportions, the curved outlines of his body and limbs, and especially his sex organs, are all childish. His height and proportions correspond with those usual at four (see p. 606 and Figs. 40 and 41).

It has been noticed that every discontinuous or major variation corresponds with some secondary or continuous variation. Thus the major variation of albinism, which stands out so conspicuously

from the normal level of ordinary skin pigmentation, may be compared with the whiteness (minor variation) which gradually results as a consequence of adaptation to a white environment, as in the arctic fox. So also the hypertrophic cirrhosis (major) of the liver which begins without cause in a young individual who has lived a perfectly normal life, and taken no alcohol of any description, corresponds, in a general way, with that atrophic cirrhosis (minor) which begins insidiously as the result of long years of persistent soaking with strong alcoholic liquors.

After the same fashion the general infantilism we term "ateleiosis," which is a primary or essential condition, a variation of extreme degree, abrupt in onset and often hereditary, has its analogue in the secondary infantilism which springs from prolonged or severe intoxication with the ferments of microphytic disease, brewing within the body, or introduced from outside. This latter, as we have already seen, is a minor or continuous variation, and is, therefore, less in degree, of more gradual onset, never hereditary, but is also prone to be associated with decided impairment in the vigour of the sexual organs.

The Course and Prognosis of Infantilism.

Generally speaking the subjects of infantilism live short lives, but to this rule there are many exceptions, and some, like Boruwlaski, are abnormally long lived. As a matter of fact, infantilism is a variable abnormality. In some cases there seems to be a real arrest of progressive development so that the individual affected gets no further than the childish or youthful stage of existence, whereas in other cases development is only stayed for a time and afterwards is renewed, puberty being postponed until the third decade. So far as we are able to judge from the cases we have seen and the scanty records, those who arrive at puberty are far more likely to live long lives than are those who do not. Indeed, it is denied by some writers that those who reach puberty and seem to possess all the essential characters of manhood or womanhood are affected with infantilism. They would regard them as dwarfs and dwarfs only. But even in these latter cases the height, proportions and physiognomy usually remain of a childish pattern. Moreover, the possession of sex and of mature ossification are not by themselves sufficient to denote manhood or womanhood, for the child of five or six with the ossification and the sexual development of an adult still remains a child, and cannot be termed a man or a woman,

despite the possession of these adult qualities. We must therefore still look upon dwarfs of the Tom Thumb pattern as examples of infantilism even though, like Boruwlaski, in their later years the facial features assume that bold, prominent character which we associate with normal maturity or senility, and though life is extended far beyond its usual limits. Though ultimately few traces of infantilism may be left, the picture presented by the morbid condition as a whole is undoubtedly that of infantilism. The defect is not one of growth alone but of development.

Ateleiosis as a Reversion.*

If an individual affected with ateleiosis be a regressive major variation he must necessarily bear comparison with other human beings who have in the ordinary course of events not yet got beyond a corresponding stage of development. In other words, there must be some definite resemblance between him and (1) undeveloped contemporary man (children) of advanced civilisation, (2) contemporary man belonging to races which have been arrested in their development, and (3) prehistoric man. At the same time it is necessary to point out that ateleiosis is a reversion, or throw-back, only because the infantile stage of development corresponds phylogenetically with the infantile stage of evolution. It represents a state of evolutionary infantilism because it is a state of developmental infantilism.

(1, 2) The resemblance of ateleiosic dwarfs to children has already been dealt with. It has also been shown that some racial infants (*negrillos* and *negritos*) are essentially children in height, proportion, and in many minor particulars.

(3) Enough evidence can be gleaned from the scanty records of prehistoric times to give us some conception of the structural and other characters of our forefathers, the children of now existing races. This evidence is to be obtained partly from skeletons and drawings and partly from folk lore.

At first sight this evidence seems to be conflicting. The skulls, or more or less complete skeletons, of the earlier palæolithic period which have hitherto been found evidently belonged to a strong and savage or uncivilised people, for they are thick and coarsely made, and their muscular prominences are conspicuous. The head is

* For most of the facts under this heading we are indebted to Messrs. Larte and Christy, '*Reliquiæ Aquitanicæ*,' to Dr. W. G. Sollas, "*Palæolithic Races and their Modern Representatives*" ('*Science Progress*,' No. 13, 1909, p. 16), to articles in the '*Journ. of the Anthropological Institute*,' '*L'Anthropométrie*,' and in other journals.

long; the forehead receding, the eye-sockets wide and deep with thick, overhanging, continuous, supra-orbital ridges, and a depression (frontal fossa) above them. The temporal ridges are high, their fossæ extensive; the nasal apertures wide, the jaws massive, the chin receding. The molars are big, and increase in size from before backward, instead of diminishing, as ours do now. The curve of the lower limbs and the condition of the joints suggest that the



FIG. 40.—Side view of the same figures; E. G— (on the right), aged 12 years, standing behind a normal boy of 6 years (see p. 606). From an *'Index of Differential Diagnosis,'* published by Wright & Sons.

usual attitude of older palæolithic man was not erect, but was more or less bending. It is of special interest that the measurements indicate that they were not small men, but on the contrary, were even bigger than we of the present day. Indeed, they are sometimes referred to as the giants of the Stone Age. Their average height, if we can judge from the meagre material at our disposal, was between 6 ft. and 6 ft. 3 in. But it must be understood that

the data from which these particulars are taken are not only derived from rare and imperfect finds, but from people widely separated from each other in point of time. One of the oldest of them, namely, the Gibraltar skull, now in the museum of the College of Surgeons of London, has been computed to date back to not less than two hundred and fifty thousand years ago.

Separated from this (Neanderthal, Mousterian) stage by an enormous interval of time was a more recent race or races of palæolithic people of the Magdalenian stage, who lived in the days of the mammoth, the cave bear, and other great mammals. Men of this period were tall, with big bones, fine open foreheads, large, narrow, aquiline noses, and powerful muscles.

When we turn from data of this kind, derived from skeletons, to those furnished by drawings and carvings, we are brought face to face with a man of very different type. In all probability the earliest carved figure of a human being yet discovered is the clay image sucked up during the boring of a well at Nampa, Idaho (Fig. 43). This image was found under a lava-cap 15 ft. thick and 200 ft. of sand and clay, the silt of an old lake. The authenticity of this find has been questioned by European authorities, but the evidence is regarded as satisfactory by American anthropologists. It has been estimated that we must go back to early palæolithic days for the date of its manufacture. Consequently we may regard it as a representation of an individual contemporaneous with the type of men whose bones have been found at Neanderthal, Spy, and Gibraltar. Yet it is amazing to find that this Nampa image is of such merit, from an artistic point of view, that it is almost inconceivable that it should be the work of the rude savages who were unable to fashion even their own weapons with any approach to delicacy of treatment. Moreover, the figure is not the likeness of a coarse and brutal type of man, but the reverse. We notice that it is naked, that its outlines are rounded, and that the hips are full, suggesting that it is the figure of a woman, though there are no breasts. What strikes us more particularly is that the trunk is long and the limbs are short, as we see plainly enough in the upper limbs, but also apparently in the left lower limb, where what seems to be the flexure of the knee points to an uncommonly short thigh.

So astonishing is this statuette that we are tempted to condemn it on its merits alone. Indeed, it is by some regarded as a votive offering of comparatively recent date and the work of Indians, who were at one time in the habit of making just such images in connection with their temple-pyramids.

Nevertheless there is further, so to say, internal evidence that the Nampa image is a genuine production of the early Stone Age. This is furnished by the etchings which have been made by prehistoric



FIG. 41.—E. G.—, aged 14 years, in his rôle of baby in "The Little Stranger" (see p. 606). From a portrait by Langfier.

Europeans upon tusks found in the cave of La Madeleine and elsewhere. Among these are representations of men and women, and some are of similar type to the individual who was the model for the Nampa image. In the earliest drawings, like that found by MM. Lartet and Christy, that described by M. Massenat, that by

M. Mortillet,* and that by the Abbe Landesque,† all the proportions are childish. In each case the limbs are short, the trunk long. In three the proximal are notably short as compared with the distal components of the limbs. The body is bowed forward upon the thighs and the knees are flexed, as if the erect attitude could not be assumed with confidence. In only one does the form of the



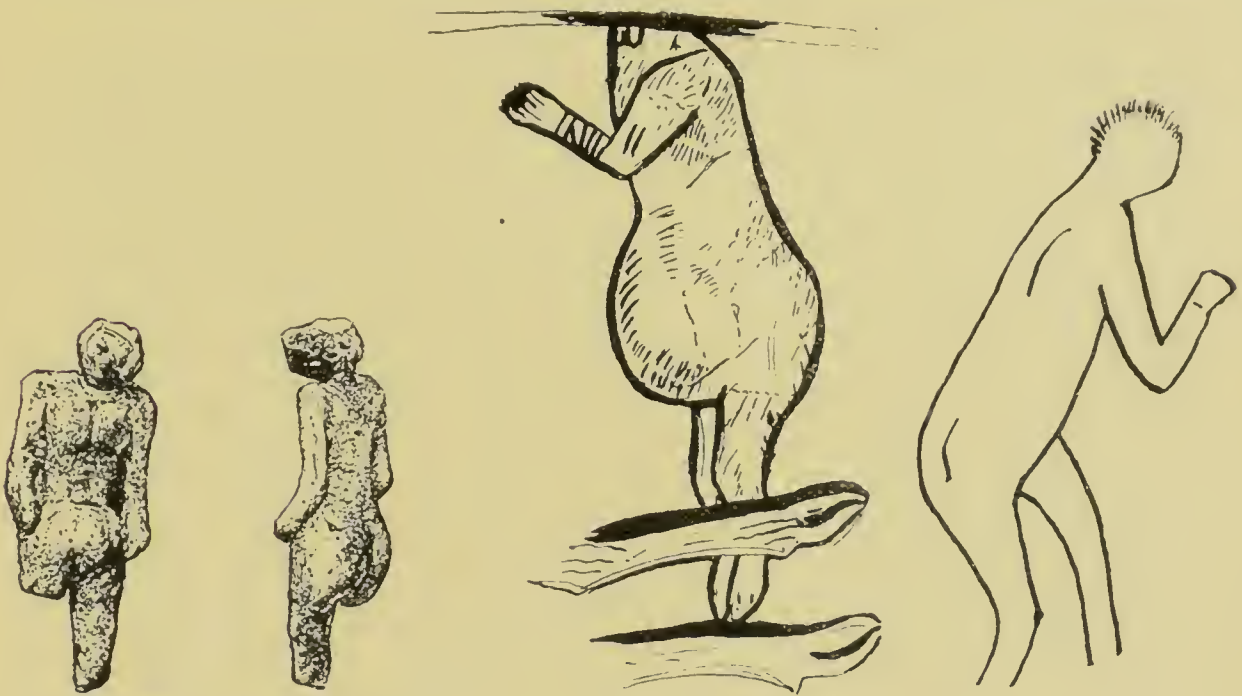
FIG. 42.—*Ateleiosis. Group III. Case 9.* Martin Lane, aged 28 years, height 4 ft. 9½ in. (1.46 m.) is standing on the right, next to him is his brother of 13, and on the left is a normal adult. The ateleiosis began at the age of fourteen. Note the absence of sexual hair, the childish sexual organs, and the youthful aspect and proportions, combined with the weathering of age (see p. 611).

skull admit of description. It is then brachycephalic. All are naked. In one, that of a woman advanced in pregnancy, the limbs are so excessively short as to suggest that the model was affected with achondroplasia, and that the drawing was cut on that account, much as achondroplastic dwarfs were chosen for their peculiarities by

* 'Musée Préhistorique.'

† See 'Men before Metals,' by M. N. Joly, p. 296.

Egyptian artists. Against this view are the facts that the limbs are not crooked, that there is no lordosis, and that the attitude is not in the least like that of achondroplasia. The vigour and skill shown in some of the drawings, and the correctness with which other figures are drawn on the same tusks, suggest that the proportions were at any rate roughly accurate. At the same time it seems incredible that the limbs could have been quite so short as they are represented in one of these figures, and we are bound to assume that the length of the body has been exaggerated. But what is perhaps most remark-



FRONT VIEW. BACK VIEW.

FIG. 43.

FIG. 44.

FIG. 45.

Clay image and drawings of prehistoric human figures.—FIG. 43.—Nampa image, actual size; from Laing's 'Human Origins.' FIG. 44.—Figure of pregnant woman with necklace and bracelet; from 'Musée Préhistorique.' Crossing the legs are the legs of a reindeer. FIG. 45.—Figure carved on ivory; from Lartet and Christy's 'Reliquiæ Aquitanicæ.' All, especially the middle figure, show a more or less childish conformation, the limbs being short, the body long.

able about all the drawings is the lightness and the delicacy of the figures. That coarseness of structure and muscular heaviness which we naturally associate with the cave-dwellers of the Stone Age are conspicuously absent. The outlines, moreover, are remarkably smooth, though there are markings on the body of the pregnant woman and markings on another prehistoric figure,* which seems for the purpose of suggesting hair.

* This is the representation of a naked man stalking an aurochs. The markings, which seem to be intended for hair, are exactly like those which are evidently meant to represent hair on the aurochs.

We have now seen that, so far as can be gathered from the meagre records, our early ancestors of early palæolithic days were, for the most part, of a good-sized, big-boned, coarse and brutish type. They were followed by, or were contemporary with, men of a tall, fine, intellectual type, with good facial characters; and living at the same time, or coming after them, were men of a totally different stamp. These were surprisingly delicate of structure, and were apparently as small made in comparison with ourselves as their predecessors were the reverse.

The explanation for this apparent discrepancy is to be found in the distribution of man and in the fluctuations of evolution.

It is quite out of the question that we should be able to trace back our beginnings along one narrow line of ancestry. It is far more likely that there never has been a time when all mankind could be grouped together into one race. On the contrary, there is every reason to believe that the evolution from anthropoid types was not only a gradual process, extending over æons of time, but was widespread, not emanating from some garden of Eden, but diffused over extensive areas of the earth's surface. If we could go back to any epoch of prehistoric time we should almost certainly find nearly as much diversity in form as there is among men, or perhaps even among monkeys, of the present day. Some would be big and muscular, depending upon strength rather than skill for their livelihood, others small and active; some of savage, brutish disposition, others more gentle; some would possess qualities calculated to send them up in the scale of development, others qualities which would gradually bring about their degeneration. Everything, in short, that we know of our prehistoric ancestry and of the process of evolution in general tends to the conclusion that there was even greater inequality of size and strength than is the case with contemporary man. As we have already seen, races of smaller and weaker peoples lived side by side with, or mingled among, races of bigger and stronger peoples. It is this juxtaposition of tall and short, of dull, stolid, physical strength, pitted against nimbleness and cunning, which accounts not only for the tales of gnomes, kobolds, fairies and other mythical dwarfs, but for the big men and giants who are so plentiful in Indian, Jewish, and Greek mythology, in Scandinavian sagas, and, indeed, in the legends and folk-stories of nearly all nations. Moreover the existence at the same time of bigger and smaller people is consistent with what is known of prehistoric interments and bone carvings, the former giving us chiefly the remains of big-boned people, such as would endure longer, and the pictures

representing a smaller, more delicately formed and artistic people, whose remains would more easily decompose.

If this view be correct it is highly improbable that reversion as a major variation should invariably take us back to only one type of our prehistoric ancestry. On the contrary it follows, almost as a matter of course, that there must be several kinds of reversions of this discontinuous nature. These varieties will be determined not only by the age of development (or period of evolution), but by the peculiarities of the stock from which the individual affected happens to spring. Moreover, in all probability, reversion is never so generalised as to repeat all characters uniformly, but is more or less partial, one character being predominant and some others following by correlation. Hence the reversion we term "general infantilism" never accurately reproduces a prehistoric individual, but may give us his general bodily configuration, leaving out important details, such as his mental or psychological characters, the colour of his skin, his hairiness, etc., yet the parts involved by virtue of correlation may be so many that a by-gone condition of the body is imitated with more or less fidelity.

In conclusion, we seem to be able to distinguish two chief types of primitive man :

One of small size, slightly built, and with a disposition of body and limbs which resembles that of a child. This seems to be the prototype of that form of reversion termed "ateleiosis."

The other, of big size, coarse build, and more simian appearance, will be referred to when we come to the subject of senilism and acromegaly.

IX

THYROID INFANTILISM ; CRETINISM

Infantilism in which there are some of the cardinal indications of cretinism is not necessarily the result of a primary deficiency of thyroid secretion. Defective action of the thyroid gland may possibly be secondary to the general infantilism. In cretinism the infantilism is very pronounced and uniform, affecting the mind as well as the body.

We occasionally meet with patients in whom defective general development combined with fatness and with a peculiar physiognomy are all suggestive of the presence of a mild degree of cretinism, though the intelligence is unimpaired. In such cases there may be no bowing of the legs, no undue susceptibility to cold, no thickness of lips or tongue. In other words, all the primary indications of cretinism and myxœdema may be absent and only some of the secondary present. These would undoubtedly constitute but a very unsafe peg upon which to hang the theory of cretinism were it not strengthened by two facts. One is that the thyroid gland is usually said to be very small; and the other is, that treatment with thyroid extract results in a striking acceleration of the rate of growth and development.

In spite of these two important indications of thyroid insufficiency, the evidence in favour of the view that the infantilism is thyroid in origin is by no means conclusive. In the first place, it is usually extremely difficult to make sure of the size of the thyroid gland by finger examination; and, in the second place, the improvement which results from the use of thyroid extract does not prove that the thyroid was the primary factor in the case, or even that it was relatively inadequate. It is quite possible that in these cases the infantilism is one of the whole body, and that the thyroid is no more affected than any other organ. If such be the explanation, it can readily be understood that the extra fillip given to metabolism in general by such a powerful catabolic agent as thyroid extract may result in a widespread spurt of development, without its necessarily following that the thyroid gland was the first cause.

One feature of these cases which seems to point to the infantilism

being general rather than local in origin is that the signs of defective general development are so much more conspicuous than those symptoms which we usually associate with the cretinous state. These latter, as has already been said, may be completely absent. Such facts suggest that the thyroid inadequacy is then only part of a widespread defect, and is not responsible for the infantilism.



FIG. 46.—*Thyroid infantilism*: A cretin, aged 20 years, with the general development usual at about 18 months. The infantilism is uniform and extreme. The intelligence, proportions, attitude, manner, are all childish. The features are puffed and disfigured with the characteristic œdema. *From an 'Index of Differential Diagnosis,' published by Wright & Sons.*

No condition is more emphatically one of infantilism than ordinary sporadic cretinism. Ateleiosis is also an infantilism of extreme degree, but whereas it is primary, cretinism is *secondary*, the initial disorder being a defective development of the thyroid gland. Both ateleiosis and sporadic cretinism are discontinuous variations, ateleiosis of the body as a whole, and cretinism of one organ of the body.

In the infantilism of cretinism an arrest of general development of pronounced degree, beginning in infancy, has such an effect as to accentuate those infantile characters which are reminiscent of that savage stage of evolution of which the baby is the phylogenetic representative.

Some of these atavistic features are well shown in the portrait. The attitude is eminently suggestive of an animal unaccustomed to an erect posture. He stands weakly, with knees half bent and feet evidently not properly accommodating themselves to the surface upon which he treads. His grasp of the bough is much more firm, and he looks round with his other hand held out for still further support. The open, loose, and expressionless mouth indicates a low order of intelligence. The stooping posture, the forward projection of the head, the protruding belly, the shortness of the lower limbs and the length of the trunk are all gorilla-like characters; so also are the prominence of the muscles of the back of the neck, and the comparative smallness of the buttock. Some of these features do not show well in the figure, but in reality combine to give a peculiarly brutish appearance to his back view. The scalp also encroaches extensively upon the forehead.

The cretinism of this boy was first observed when he was about six months old. The portrait shows him at the age of twenty years. He was then able to walk, was affectionate, had with much difficulty been taught to be clean in his habits, wore short frocks, cried when in pain or discomfort, was able to say "mother" and a few other infantile words, and could feed himself.

We are indebted to Dr. Charsley, of Slough, for this case.

SECTION VI

Morbid Acceleration of Regressive Development or Senilism

I

INTRODUCTION

Premature senile decay is usually based upon a prior infantilism. Presenility must be distinguished from shortness of life due to impaired "nutrition." There are two types, the fat and the lean, but the best division is into racial and individual. Individual senilism occurs either as a minor or as a major variation.

Causes and Classification of Senilism.

We have seen that normal human development is a continuous process, beginning at birth (the before-birth being pre-human), rising to a climax in middle age, and falling through second youth, second childhood, and second infancy to the second birth, which is death.

We have seen also that if from any cause the ascending stages of development are unnaturally curtailed the whole cycle of development is apt to be shortened. Hence the causes of defective development are also the causes of premature old age. Not much, therefore, need now be said about the ætiology of senilism, seeing that it has already, to some extent, been discussed when we entered upon the subject of infantilism.

And even if, for the time, we put infantilism on one side and fix our attention exclusively upon those factors which do not come into operation until middle age, we shall still find that they are usually of the same nature as those which are responsible for infantilism. Adaptation, correlation, intoxication, all play their part in a similar way and to a similar degree in inducing old age as in delaying development. Nothing, perhaps, shows this better than the effect of loss of the thyroid secretion upon progressive and retrogressive

development respectively. So different is the result of this same cause acting at different ages that for a very long period no one was able to see any connection between them. Acting upon development during the earlier stages of life, the result is a form of infantilism, which we term cretinism; but the same secretion cut off during the declining stages of development leads, not to infantilism, but to a form of premature old age, which has very rightly received the totally different name of "myxœdema."

It follows as a necessary consequence to our conception of development that the more pronounced and persistent the infantilism the earlier will be the senilism which results from it. Infantilism which begins in youth will sometimes give rise to premature old age, but this old age will not come on so soon as when the defective development begins in childhood, nor will this, again, be so frequent or so rapid as that which starts in infancy. In all cases the earlier in life the degeneration sets in the more emphatically is it a disease, the more disastrous its consequences.

In estimating longevity it is important to bear in mind that nutrition "rather than development may be at fault. The short-lived tendency is not shown merely by a tendency to die at an early age from ill-defined conditions coming under the head of general breakdown, but by a lack of resisting power, a tendency to die from ordinary ailments through which other people pass without much danger."*

In any given case it may be very difficult to say whether premature death be due to a primary failure of nutrition, or to a failure of nutrition itself the consequence of too early senility. As a matter of fact we can hardly be justified in regarding any particular case as one of senilism unless there are obvious signs of senile decrepitude.

Kinds of senilism.—There are many different kinds of senilism. Regarded from the point of view of causation there are two sorts: *primary* and *secondary*. It is primary when it begins in an individual of normal development, and secondary when it starts in a subject who is already affected with infantilism.

Two types of infantilism were referred to, namely the *Brissaud* or *myxœdematous type* and the *Lorain* or *cardio-vascular type*.

We also can distinguish these two types in normal old age and (to an exaggerated degree) in senilism. In the one, corresponding with Brissaud's type of infantilism, the individual becomes fat, puffy, bloated, lethargic; in the other, corresponding with Lorain's type of infantilism, he is lean, wiry, and often emaciated, so that

* 'The Hospital,' 1898, p. 395.

his tortuous temporal arteries stand out pulsating and conspicuous under a thin covering of dry integument. In fat old age sexual vigour declines at an early stage, so that sterility is one of its chief features, and there is often reason to suspect early degeneration of the thyroid gland. In lean old age the functions of the reproductive organs and of the thyroid gland are retained much longer—in men sometimes almost until the end of life. Of the two types—the fat and the lean—the former is apparently the more abnormal, for those who become grossly obese after middle age are notoriously short-lived, whereas those who become dry and shrivelled tend to live long.

For descriptive purposes and for the sake of uniformity it is best to divide senilism into two classes :

I. Evolutionary or racial, and—

II. Developmental or individual.

I. Evolutionary or Racial Senilism.

There can be no doubt that the duration of life of human beings tends gradually to increase. Notwithstanding the mythical ages of the Bible patriarchs, we have every reason to believe that old age began earlier with the Jews of pre-Christian time than it does now. Even in the middle ages the senile period of life according to Montaigne and Hampole (see p. 14) began before fifty, whereas nowadays we do not, generally speaking, regard a man as old until he has passed sixty.

It is in keeping with this fact that the duration of life in racial infantilism is decidedly shorter than is the duration of life in nations which have attained full development. Of the Bosjesman dwarfs Burchell * writes : “ In five or six years after their arrival at true manhood the fresh plumpness of youth gives way to the wrinkles of age,” and much the same is said by other travellers, not only of Bosjesman, but of Australian and other inferior races. Bosjesman and Central African dwarfs are said to succumb to old age about the age of fifty, and, so far as is known, some of the anthropoid apes have a similar duration of life.†

II. Developmental or Individual Senilism.

In this form of senilism it is often very difficult to decide which of the two factors is the more important, to wit, a latent tendency to

* Rev. J. G. Wood, ‘ Natural History of Man,’ vol. i, p. 272.

† Huxley (‘ On the Natural History of the Man-like Apes’) says that the orang probably lives to forty or fifty years.

die young, or the influences of an ageing environment. In some cases the surroundings are of such a nature as almost to be sufficient by themselves to induce premature senility; but as a rule the cryptic, hereditary factor is of still more consequence.

Regarded from this aspect, abnormally premature old age or senilism exists in two forms. In the one it is due partly to environment and partly to an inherent tendency to prematurity; in the other the tendency to die early exists alone independent of environment. In the former the general senilism is (1) a minor or continuous variation; in the latter it is (2) a major or discontinuous variation.

II

GENERAL SENILISM OCCURRING AS A MINOR OR CONTINUOUS VARIATION: SYMPTOMATIC SENILISM

As a minor variation senilism is either adaptative or correlative. When adaptative the cause is in the environment, and consists in either defective sanitation in general, or in some internal intoxication (internal environment).

THOUGH the causes of senilism and of infantilism are fundamentally similar in character their effects are as a rule far more precise when they give rise to infantilism than to senilism. When, owing to an attack of enteric fever, an individual of, say, twenty, resembles in his development a youth of fifteen, the relation between cause and effect is very evident. But when a man of fifty has enteric fever, and dies from old age at sixty-five instead of at seventy, the connection between the enteric intoxication and the premature old age, though perceptible, is not obvious. We cannot say that his life would not have ended at sixty-five if he had had no enteric fever. Still less can the effect be traced of other forms of adaptation or of correlation, though if we can judge from analogy they must have as great an effect in the induction of senilism as of infantilism.

One explanation of this difficulty in tracing the connection between cause and effect is that the life which starts abruptly at birth is naturally so variable in respect to the age of its termination that it may very well be considerably entailed, and yet not fall short of the general average of longevity.

Another important reason for haziness as to the cause of some cases of senilism is that as regressive development sets in more than one cause may be at work, and these causes may be still further augmented as the years pass on, making it very difficult to say which is the most important.

These and other reasons account for the rarity with which cases of premature old age are recorded. Generally speaking only the most sensational cases of senilism find their way into the pages of medical publications, the fact that a man dies prematurely old at,

say, fifty-five or thereabout, not being thought worthy of special account.

While the blighting of almost a whole existence by infantilism is a serious matter, the cutting short of a man's life by a few years is proportionately trivial. Hence senilism must be very pronounced to come under the definition of abnormality. Still more rarely is it sufficiently marked to constitute disease.

Senilism as a minor variation may be the result either of adaptation or of correlation.

A. Adaptative Senilism.

This, like the corresponding form of infantilism, may be the result of (a) general insanitation, or of that more localised and concentrated insanitation known as (b) intoxication by micro-organisms.

(a) *Senilism of Insanitation.*

Under this heading we comprehend not only morbidly premature old age the result of bad air, rotten food, and filthy surroundings, but all other depressing, or otherwise unhealthy, conditions which may encompass a man from the physical or the mental or the moral aspect. Hardship alone, even when congenial and counterbalanced by the bracing and inspiring influence of success, seems capable of seriously curtailing the natural duration of life.

Archibald Forbes* specifically attributed his premature decrepitude to the over-fatigue and hard living of his life as a war correspondent, and Stanley,† though less definitely, accounted for the breakdown of his extraordinary capacity for endurance and of his robust physique to the hardships incidental to his African travels, supplemented by malaria. (See also p. 36.)

Of still greater potency in promoting senescence are insanitation combined with circumstances, such as defeat, or imprisonment, calculated to produce mental depression. Indeed, there can be no doubt that depressing circumstances alone, if prolonged or acting in a concentrated form, are capable of curtailing development by precipitating old age before its time. Further, though no actual example can be quoted, it can hardly admit of question that senility so produced occasionally sets in so early as to present all the features of abnormality, such as we have observed in local senescence

* 'English Illustrated Magazine,' 1884, p. 456.

† 'Biography of H. M. Stanley,' by Dorothy Stanley.

of the kidney or liver. In other words the old age may be so premature as to justify the denomination of senilism. (See also p. 36.)

(b) *Toxic Senilism.*

Though no specific instance of actual senilism so produced can be quoted, the influence of the toxins in inducing senile decay admits of no question. As we have already seen, two factors are requisite for the production of morbid (premature) senility or down-right senilism, the one being the toxin, and the other a latent tendency to succumb to premature old age. When these two—the latent variation, and the favourable environment—act together, it can hardly be doubted that they are occasionally responsible for the onset of a general senilism which is as truly a disease condition as is fibrosis of the liver or kidney.

Influenza, enteric fever, syphilis, gout, lead, alcohol are amongst the chief promoters of presenility.

The wizened appearance of infants affected with *syphilis* of intra-uterine origin is often commented upon. Probably in most cases it is a mere surface symptom, affecting the appearance only, and due to the fact that the infantile state is in some respects so like the senile state that when emaciation is added to infancy the likeness is enhanced and becomes patent to everyone.

But occasionally, as we have already seen, syphilis of congenital origin is a cause of genuine infantilism, and when this is the case senilism is prone to supervene. We shall presently give some details of the celebrated case of the dwarf Béb  (p. 637), in whom syphilis may have been responsible both for senilism and for the infantilism from which it sprang.

III

GENERAL SENILISM OCCURRING SOMETIMES AS A MAJOR, AND SOMETIMES AS A MINOR, VARIATION: CORRELA- TIVE SENILISM

Correlative senilism exists when the whole body becomes senile as the result of the premature degeneration of one or more organs, such as the sex organs or the liver, or kidneys. Senilism is perhaps most often the result of mixed causes, of which the celebrated French dwarf Béb  is an example. His premature senility was probably the combined result of syphilis, microcephaly, and general infantilism.

THIS form of senilism occurs when one, or more than one, organ undergoes premature senile changes and induces a breakdown of the whole body by association or correlation.

As a matter of fact this kind of senilism is purely academic, for it is not possible to say whether the developmental anomaly of the organ is the cause of the general senilism or whether the local trouble ensues as the first symptom of generalised premature old age.

A case in point is described on p. 274, where an account is given of a patient with hypertrophic cirrhosis of the liver, who first became conspicuously senile while affected with the disease, and underwent a process of as rapid rejuvenation after it had been cured. Before treatment she was thin, haggard, feeble, and her hair was of a uniform glistening white, so that she looked sixty-five or over when she was in reality only forty-eight. Within a year of being rid of her cirrhosis she had so changed for the better that it was not easy to recognise her as the same individual. Perhaps the most conspicuous change was in the appearance of her hair, which had resumed its coal-black tint, but was saved from the suspicion of having been dyed by the presence of occasional white hairs.

Of course, it is obvious that the symptoms produced by the cirrhosis might have been enough, by themselves, to give rise to senility, so that there seems no need to invoke the assistance of correlation to account for it.

It can only be said in general terms that the appearance of

cirrhosis, of arterial sclerosis, of cancer, chronic Bright's disease, or of some other local degeneration is sometimes followed by such rapid breakdown of the whole body as to suggest that the general senile decay is induced, not so much by any direct cause, as reciprocally, that is, by correlation.

Further, and perhaps more satisfactory, instances of correlative senilism will be given when we come to senilism as a major variation.

Senilism Associated with Sexual Precocity.

One of the mixed causes and accompaniments of premature old age is abnormally early appearance of the sex functions.

It is highly probable that some cases described as sexual precocity are in truth primarily an acceleration of the development of the whole individual, causing him to run through the phases of life with extraordinary celerity. In a curtailed existence the ripening of the organs of sex might very well occur at such an early stage as to lead to the impression that they were the leading factor of the situation, and that the generalised prematurity followed suit. In all likelihood the relations between the sexual and the general precocity are sometimes of the one kind and sometimes of the other.

Probably the earliest examples of this senilism of sexual precocity on record is that of a case spoken of by Craterus,* brother of Antigonius, who was successively infant, youth, adult, father, old man, and corpse within seven years.

Other more or less apocryphal instances are referred to under the heading of "sexual precocity" (p. 522).

Dr. Kiernan, of Chicago, in a suggestive paper† on anomalies of development due to intra-uterine periods of stress, dwells upon the importance of precocity of either mind or body as a cause of premature senescence.

As a good example of the truth of the old adage "early ripe, early rotten," he refers to the history of Louis II of Hungary, who was crowned in his second year, became sexually mature and had a well-grown beard at fourteen, married at fifteen, had grey hair at eighteen, and died at twenty.

The following is a case of the association of pronounced sexual precocity, with premature senility. Not enough particulars are, however, furnished of this latter condition fully to justify the diagnosis:

* 'Phlegontis Tralliani de Mirabilibus et long. lib.'

† 'Journ. of the Amer. Med. Assoc.' vol. xxxvi, 1901, p. 1270.

It is that of Thomas Hall, "the fat boy of Willingham," of whom an account has been given by Mr. Almond, a clergyman, and by a surgeon named Dawkes. The latter, after the death of the prodigy, wrote a book about him.* He was born on October 31st, 1741. His father was short, while the mother, who was Mr. Almond's servant, was a healthy, well-formed woman. She died suddenly when her baby was nine months old, apparently as the result of exhaustion from over-suckling. Thomas was the second boy, and was not unusually big at birth; but when nine months old the parts of generation began to develop to a surprising extent, and he began to grow prodigiously. He was two years and eleven months old when Mr. Almond first wrote about him, and was then "3 ft. 9 in. (114.4 cm.) high, and every part in proportion thereunto; his strength and courage such as overcame boys of six, seven, or eight years of age; his voice like a man's, very gross, weight above 4 st. (25.49 kg.), and he appears to have as much understanding as a boy of five or six years old; and what is most surprising is his penis, which is four inches long when erect; the hair on pubes an inch long and thick." The midwife told Mr. Dawkes that the child at birth was "not more than a lusty boy, save that the parts of generation were remarkably large, and that the lanugo first appeared when he was a year old," which, she added, "gave great uneasiness to his parents, who were very religious people."

The hair on the head was long, strong, and dark brown, and displayed itself naturally in fine curls. Mr. Dawkes saw him take up and throw from him with much facility a blacksmith's hammer which weighed 17 lb., and he was able to lift also 12 st. He was of quick apprehension and had a retentive memory.

He was now lost sight of for two years, but Mr. Dawkes, when he saw him again in November, 1746, noticed between the nose and upper lip conspicuous "whiskers" of a dark brown colour, but not a single hair on the chin or sides. About this time he began to cough, and was said to have consumption. Some eight months afterwards "the disease made such havoc with the muscular fibres, which rapidly wasted, and produced such alteration in his features as had very little impeded the calcification of bones." "He died as of extreme old age on September 3rd, 1747. He was then 4 ft. 6 in. (137 cm.) in height, and upward of 7 stone (44 kg.) in weight." "From his birth until three years and two months old was the most rapid time of his growth, and the next two years he only grew eight

* 'Prodigium Willinghamensis,' also 'Philosophical Transactions,' 1745, and the 'Gentleman's Magazine,' January, 1745.

inches, and the next eight months one inch. Before he died he had the appearance and manners of a very decrepit old man."

Senilism of Mixed Origin.

(1) *Syphilis, Microcephaly, and Infantilism, ending in Senilism.*

It has been shown that the most striking cases of prematurity are those which result from the action of more than one cause. The one agent then reinforces the other. Thus we saw that when syphilis is a degenerating agent it is far more effective if combined with alcohol; and when, in addition, the deteriorating influences of a perverted civilisation are brought into action the combination is peculiarly dangerous, and accounts for many cases of general paralysis, tabes and other degenerations.

So, in the same way, when syphilis is accompanied with some other cause of general prematurity the combination is calculated to produce a far greater effect than when either of the two acts separately.

In the following celebrated case* of the French dwarf Nicholas Ferry, or Ferry, called Bébé, there seems to have been a combination of congenital syphilis with microcephaly and infantilism, but whether the syphilis caused the microcephaly or the infantilism or was merely coincident with them it seems impossible to say.

At the time of his birth Nicholas Ferry was said to have been between 8 and 9 in. (21–23 cm.) in length and weighed 12½ oz. (361 gm.). In July, 1746, when four and a half years old, he was measured by Dr. Kast, who found him to be 22 in. (61 cm.) long and 9 lb. 7 oz. (4·280 kg.) in weight. His nose was aquiline and well formed and his eyes were of a deep brown colour. His abdomen was large when compared with his chest. He was possessed of extraordinary vivacity, and did not rest a moment in repose.

When three months old he had smallpox and afterwards came under the protection of Stanislaus, King of Poland, by whom he was called Bébé. He was then said to be 15 in. (41·25 cm.) high, and 13 lb. (5·895 kg.) in weight. His person was also described as agreeable, well-proportioned,† and in perfect health, though his reasoning faculties were "not superior to those of a well-taught pointer." This however, is undoubtedly but a picturesque exaggeration, for though

* 'Histoire de l'Académie Royale des Sciences,' an. mdcclvi, "Observations Anatomiques," viii, p. 44; also 'Mémoire sur un nain' (Bornwalski), par M. le Comte de Tressan, 1760.

† Either this last statement or the measurements are incorrect, for the height of a new-born baby is 51 cm., and the weight is 3 kg., so that a child of 38 cm. high and weighing just double this weight can hardly be termed well proportioned.

“he had no sense of religion,” he was capable of talking intelligibly and of “imperfectly learning music and dancing.” He was susceptible of passion, particularly of anger, jealousy, and the “*désire ardent*.” When sixteen years old Bébé was only 21 in. (57·75 cm.)* in height, but still healthy and well proportioned. At this time puberty produced upon him a great change: his strength began to decrease; his spine became crooked, his head fell forwards, his legs were enfeebled, one shoulder-blade projected, he lost his gaiety, and became a valetudinarian. His stature increased 4 in. (11 cm.) in the four succeeding years. Count Tressan foretold that he would die of old age before he was thirty, and in effect he did so, for at twenty-one he was shrunk and decrepit, and at twenty-two he could, with difficulty, make a hundred steps successively. In his twenty-third year he was attacked with a slight fever, and fell into a kind of lethargy, in the intervals of which he spoke with great difficulty. These diseases soon proved fatal, for he died on June 9th, 1764, at the age of twenty-two and a half years. For the last five days of his life his ideas seemed to be more clear than when he was in health. At the time of his death he measured 33 in. (89 cm.) in height.

A representation of Bébé was modelled in wax. A few years ago, when we saw it, this model stood in the Orfila Museum of the School of Medicine in Paris. It was made under the supervision of a surgeon who had attended Bébé for several years. It shows how he appeared at the age of eighteen, with the hair arranged in the fashion of the day, and in his own clothes. Its appearance hardly tallies with the description which has been given of him when he was approaching this age. It is 72·5 cm. high. His figure is fairly erect and his expression pleasant, and he looks well nourished, and by no means senile or debilitated. On comparing this figure with the skeleton (93·5 cm. high), and making every allowance for the rapid changes which took place after he was eighteen, there can be no doubt that the head has been made too large, and the neck too short, and that the whole figure is much too thick-set to be a true likeness.

In the accompanying portrait the countenance is very different from that of the wax model. The rest of the figure is also much more slender and graceful, and its proportions are such as we might expect from the appearance of the skeleton. It closely corresponds

* There is a discrepancy in these figures, for he was said to have been 22 in. (61 cm.) high when measured by Dr. Kast at the age of four and a half years, and at death 33 in. (89 cm.), whereas his skeleton measures 93·5 cm. His height at death must therefore have been quite 95 cm. (37½ in.).

with the portrait in pastel at the Nancy Museum, reproduced by Garnier,* but the proportions of the former are evidently more correct.

On *post-mortem* examination of his body there was found to be



FIG. 47.—Bébé. Figure enlarged from portrait engraved on memorial card. Though of about the height of a child of four he has the proportions of a man.

water in the chest, and the lungs were adherent to the pleura in several places.

In the skeleton attention was drawn to the enlargement of the nasal bones, an accentuation of the natural curves of the vertebral column in the lumbar and dorsal regions, and to its very advanced

* 'Les Nains et les Géants,' p. 157.

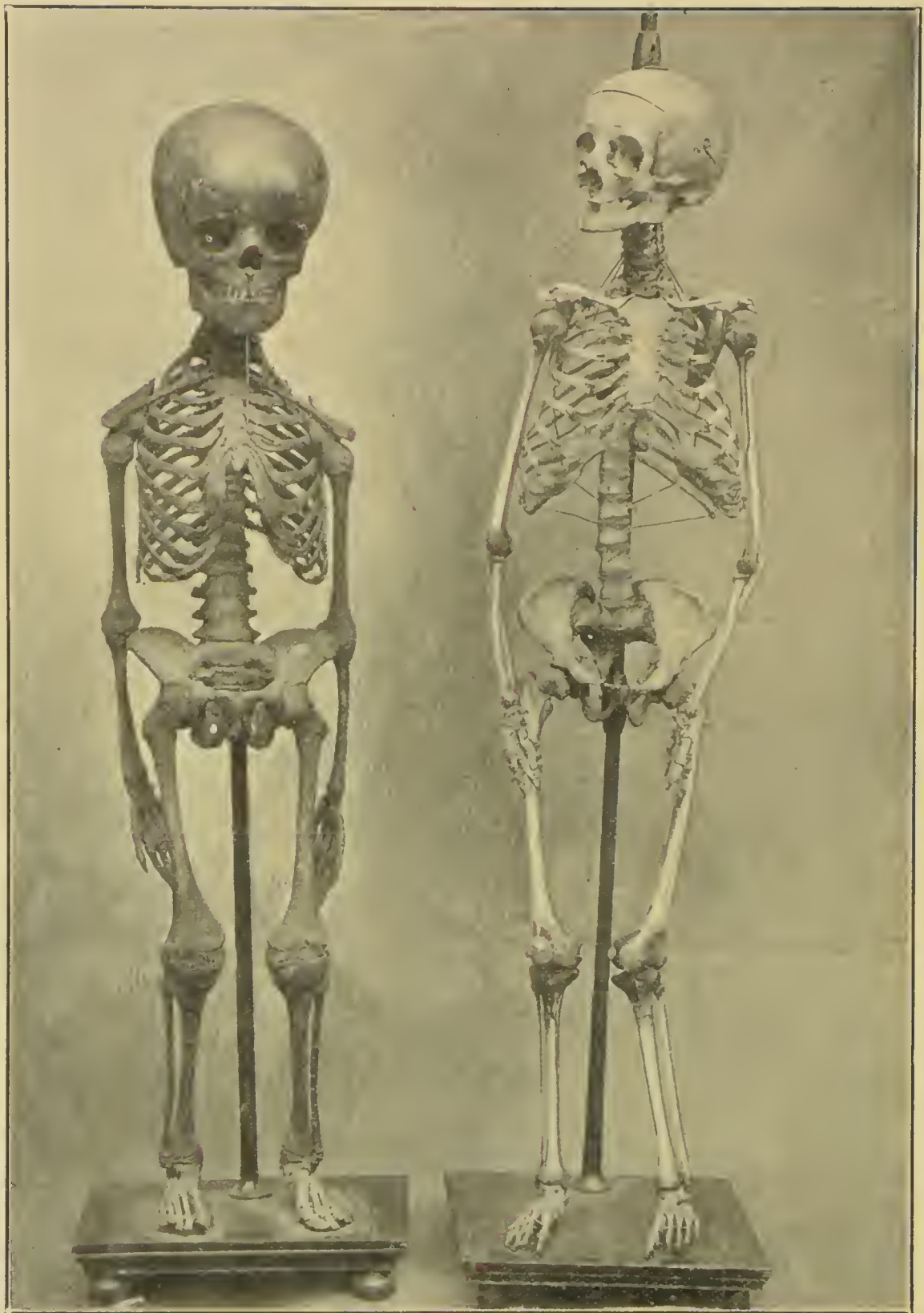


FIG. 48.—Skeleton of Bébé, aged 22½ years, standing beside the skeleton of a child of 3¼ years. Bébé's skeleton is only a little taller than that of the child, but is formed on an adult model. The head is too small, the bones are delicately made, and the hands and feet are conspicuously little. Note the large and projecting nasal bones and the toothless, senile jaws. The clavicles of the child are too sloping, and allow the hands to come down too far on the femora.

state of ossification. It was pointed out that there was no vestige of a suture between the frontal and parietal bones, and that the bones of the vault were in some places exceedingly thin, especially towards the occipital region. Porous bosses were described on the occipital bone.

The skull (13 cm. long, 11 cm. broad, 38.3 cm. circumference) is imperfectly divided into its two tables in the thickest parts only. It varies in thickness from a paper-like tenuity in some places to 3 mm. in others, but over the rough porous bosses it amounts to 7 mm. These bosses are situated on the posterior parts of the parietal bones, and cover almost one quarter of their surface. "The lambdoid suture is fused at the left posterior inferior angle. In the neighbourhood of the auditory meatus the bone has a spongy aspect indicative of an osseous lesion" (Porak). The base of the cranium is normal.

The history of the case is indicative of the presence of both lateral and antero-posterior curvature of the spine. The skeleton shows a remarkable curve of the whole of the dorsal and lumbar regions to the right, with slight rotation and a slight compensatory curve in the cervical region. This is apparently not due to any unevenness in the deposit of intervertebral substance. There is no very noticeable exaggeration of the antero-posterior curves. The upper half of the sacrum projects backwards too abruptly, while the lower is doubled forwards at a sharp angle, carrying the coccyx with it.

Besides the indications of premature or excessive ossification which are presented by the above bosses, by the fusion of the parietal bone, and by the large size of the nasal bones, the same fact is shown in the union of all those epiphyses which are usually separate between the eighteenth and twenty-fifth, and between the twenty-fifth and thirtieth years. Even the upper sternal epiphysis seems to be partially united.

Other senile characters are to be found in the jaws and in the upper ends of the femora. In the jaws the teeth are absent, and there is consequent absorption of the alveoli and projection of the chin. In the upper jaw the alveolar margin is rough, and a few imperfect tooth sockets are still present. The mandibular angle is somewhat obtuse, but cannot be said to present senile features. The angle of this bone is everted by muscular attachment. The neck of each femur is short, and the angle it makes with the shaft is but little more than a right angle. But it has been shown by Sir G. M. Humphry that the angle is naturally smaller in short than in tall people.

Dr. Porak, in the course of a description of the skeleton of Béb , says that he drew the attention of Prof. Fournier to this case, and that the latter pronounced it to be undoubtedly syphilitic. Prof. Fournier pointed out that beside the stunted growth "one can connect with this malady the parietal lesions, the childishness, the early falling of the teeth, the lesion of the external auditory meatus, and the death coming on at an unusually early age." "The parietal bosses are exactly like the gummatous symmetrical periostitis of early life with natiform depression of the skull." To these we may perhaps venture to add the tabetic depressions of the skull.

Sir G. M. Humphry * pointed out that "in B b  the leg and forearm are short, the arm long in comparison with the whole figure, and the thigh is long in comparison with the leg."

But next to the stature of the skeleton (equal to that normal to a child of four) the smallness and delicacy of the bones and the indication of senility, we are most struck with the smallness of the head and face, the circumference of the head (38.3 cm.) being very little more than the circumference of the head of a new-born child (33-34 cm.).

Though this case is now given as a minor variation, induced by syphilis, there is much to be said for the view that it was a major variation, or that the syphilis was no more than a casual accompaniment.

The microcephaly was symmetrical, and in other respects corresponded with the "spontaneous" form as described by Tanzi. It seems very likely that this microcephaly in turn gave rise by correlation to the infantilism just as we have seen occurs in some other small-headed dwarfs, and all acted together to precipitate the early senile decay.

* 'The Skeleton,' p. 151.

IV

THYROID SENILISM: MYXCEDEMA

In myxœdema premature senile decay is not, in the first place, a generalised affection, but is merely incidental to the senilism of the thyroid gland as an organ.

THE best example of secondary senilism is without doubt *myxœdema*. The loss of hair and teeth, the dry, harsh skin, susceptibility to cold, slow speech, impairment of memory and mental processes in myxœdematous people are essentially senile in character, and nothing is more striking than the rejuvenation which takes place when the patient is restored to health by means of thyroid extract.

We have recently had under our care a lady who became so affected with myxœdema that at the age of forty-five relatives who had not seen her for about two years not only failed to recognise her, but for a time could not believe that the stout, pink-and-white faced, dowdy-looking bewigged woman of deliberate speech was indeed the lively, black-haired, thin woman they had so recently seen. Later on, under the influence of thyroid extract, the usual marvellous rejuvenation took place. The sparse grey hair barely covering an almost bald head gave place to a thick, close crop of coal-black stubble, she again became thin, and her speech, manner, disposition, all underwent an alteration for the better, so that within the space of less than a year it was remarked that she looked nearly twenty years younger.

The senescence of myxœdema is more than a mere simulation. There is a corresponding tissue change, so that premature senile degeneration of the kidney (chronic Bright's disease) or of other organ is prone to occur, or some chronic bronchitis or pneumonia sets in, and carries off the more or less decrepit patient after the same fashion that it terminates the existence of so many normally senile individuals.

Hence it is that though both cretinism and myxœdema are alike due to defective action of the thyroid gland and act in identically the same way, they are such widely different diseases.

The one shows itself as stereotyped youth, the other as premature

old age. So different, indeed, are they that it did not occur to anyone to connect them together, much less to look upon them as the same disease, until a knowledge of the action of the thyroid gland had paved the way for the recognition of their essential identity.

Now that we are alive to their pathology we do not fail to notice their common characters. We at once observe the morbid state of the thyroid gland, the puffiness of the skin, the thickness of the tongue, the clouded intellect, and other features common to both forms. But before their identity was established the symptoms which most attracted attention were the persistent childish configuration, the baby-like intelligence, the bowed legs of the one, and the grey, almost bald head, the stooping figure, the sluggish intelligence, the slow speech, the poor circulation, and the dry, harsh skin of the other. The one set of symptoms pointed, in short, to defective development, while the other betokened the onset of premature senility, and we can hardly wonder that our predecessors were puzzled and failed to recognise the two aspects of a disease which at one age blew hot and at another cold with the same breath.

V

GENERAL SENILISM AS A MAJOR VARIATION; SECONDARY SENILISM: PROGERIA

Morbid acceleration of regressive development (senilism) is sometimes consecutive to, or accompanies, infantilism. This occurs as a major variation in progeria. Progeria, like ateleiosis, varies according to the age of its appearance. In its most characteristic form it begins before puberty, and is manifested by the rapid advance of old age in one who is in a conspicuous state of defective development.

Introduction.

We have seen that generalised premature senile decay may, like defective development, be—

(1) A mere natural variation, as when it affects a man who enters upon his dotage at, say, from fifty-five to sixty;

(2) Or it may be a manifestation of disease—senilism—and then be either one of the symptoms of some anterior morbid tendency, and constitute a minor or continuous variation;

(3) Or it may manifest itself in such an outstanding form and so unexpectedly as to constitute a major or discontinuous variation and a disease in itself. It is this last form of senilism which we now have under consideration.

It must be evident that this second form, or essential senilism, like the corresponding form of infantilism, will vary in its manifestations according to the time of life at which it begins. We should, at any rate, expect that senile decay setting in after the age of forty will not be so pronounced as senile decay starting between twenty and forty, and that again will present a very different aspect from the senility of pre-pubic days.

But no circumstance produces such striking changes in the manifestation of premature senile decay as a prior infantilism. When dealing with the disorders of *cells* we saw that nothing conduced to senility (cancer) like a previous arrest of development. And when *organs* were under consideration it was noticed that an infantile state constituted a strong predisposition to pre-senile

degeneration. So also with the *whole man*, morbid defect of development markedly facilitates the entrance into a state of senilism, and strongly tinctures its whole aspect and course. Indeed, we may say that the presence of infantilism so stamps the secondary or consecutive senilism which arises out of it as to divide it more or less sharply from the other or primary form, and to constitute a distinct type. Hence general senilism as a major variation is of two types—the secondary or infantile type, and the primary, or, as we shall presently see, the acromegalic type.

But even now we have not arrived at the limits of our division, for there is reason to believe that senilism, the outcome of infantilism, may be of two varieties.

The two—infantilism and senilism—may arise and run their course together.

Or the infantilism may come first and the senilism be consecutive to it.

Moreover, each of these forms is liable to modification according to the age at which it begins, or the character of the infantilism to which it is consecutive.

Generally speaking, the earlier in life the infantilism begins, the earlier and more pronounced is the senilism which is associated with it.

Let us now take simultaneous infantilism and senilism first, and afterwards deal with consecutive senilism.

I. Simultaneous Infantilism and Senilism—Progeria.

Progeria arising in Infancy or Early Childhood.

This constitutes a disorder of exceedingly pronounced type. So far as we know only three examples have been recorded.

One of these came under our own observation from the age of fourteen till his death, four years later, when a *post-mortem* examination was made. The other had been seen by Sir Jonathan Hutchinson when he was three and a half years old, and was then described by him under the title “congenital absence of hair and mammary glands, with atrophic condition of the skin and its appendages, in a boy whose mother had been almost wholly bald from alopecia areata from the age of six.” And the third has just lately been described by Dr. Variot and his assistant, Dr. Pironnean, of Paris.

Sir Jonathan Hutchinson most kindly permitted us to follow up

his case. This boy was fifteen years old when we first saw him, and he died two years later.

The salient features of these two cases were remarkably alike. In



FIG. 49.—*Progeria. Case 1.*—Aged $1\frac{1}{2}$ years. From a photograph taken about one year after the disorder was first noticed. He looks thin and wizened, and much of the hair has gone. The size of the head and the downcast appearance of the face suggest hydrocephalus. But the former was probably only relative, the result of wasting of the face, while the hanging down of the head was due to weakness of the neck-muscles.

fact, so closely did these two beings resemble one another that when permission was asked of the father of the second case to take a photograph of his son, and a portrait of the first case was produced

to show what was required, the father at first supposed that he was gazing on the nude figure of his own son.

Hence it is only necessary to run over the chief characters of



FIG. 50.—*Progeria*. Case 1.—Aged 7 years. He is bald, and looks older than his years. The photograph has been much “touched up” by the photographer.

the first case in order,* with one or two important differences, to describe the second.

CASE 1.*—No cause could be discovered, either in the patient or in his family, and a series of photographs showed that the disorder began in

* For a full description see ‘*Med.-Chir. Trans.*,’ vol. lxxx, 1897, p. 17; also ‘*The Practitioner*,’ vol. lxxiii, 1904, p. 188.

infancy and was progressive. The most striking features next to the size (height 113 cm., weight 16 kg.), were his extraordinary leanness (which revealed his nasal cartilages, veins and tendons with startling clearness), and



FIG. 51.—*Progeria*. Case 1.—Aged 17 years. Note the skinny, beaked nose, revealing the outlines of cartilages, the thin lips, ill-developed lower jaw and clavicles, wasted ear lobules, and the scanty white hair: also the extreme leanness, the poor muscular development, the large knuckles of the hands, the absence of sexual hair, and the backward sexual development. A normal adult hand is introduced to show the proportions.

his general aspect of senility. Save for a sparse growth of fine grey hair on his scalp, eyebrows and eyelids, he was destitute of hair. His skin was thin,

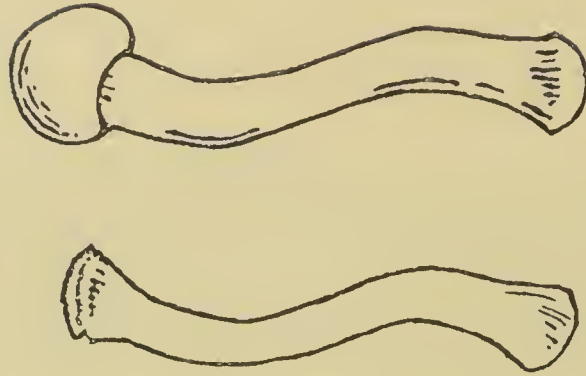


FIG. 52.—The top figure represents the clavicle of A. R—, the lower figure the clavicle from a new-born child, both of actual size. The glistening cap of cartilage on the sternal end of the former reminded one of the glass head of a shawl-pin.



FIG. 53.—*Progeria*. Case 1.—Aged 15 years.

dry, and old-looking, nails short, flat, membranous, and muscles poor and weak. He stooped slightly when walking, and liked to walk with a stick.

At the same time he presented many childish and infantile features: thus, his anterior fontanelle was not closed; there were still many milk



FIG. 54.—*Progeria*. Case 2.—Aged 15½ years. The senile attitude and prominent, staring eyes are better shown in this portrait. The narrow chest, due to smallness of the clavicles, full belly, and strongly curved femora are also very evident. (Sir Jonathan Hutchinson's case.)

teeth crowded among some of the permanent set, causing the alveolar border of the lower jaw to project: the voice was piping; the genital organs a year or two behind-hand; and, as we have already implied, his stature was childish. After death the same curious mixture of youth and old age was observed in his internal structure. He died at the age of eighteen, with sym-

ptoms suggestive either of thymic or cardiac asthma, and it was subsequently found that he had a persistent, enlarged, and fibrous thymus gland, and that there was extensive atheroma of his mitral and aortic valves. Moreover, his coronary arteries were completely blocked, and could with ease be



FIG. 55.—*Progeria*. Case 2.—Aged 15½ years. Notice the extreme emaciation and the conspicuous ribs, veins, and tendons. The abdomen is full, and the patellæ are pushed forward by the relatively big lower ends of the femora. The normal adult hand is introduced to show the proportions. (Sir Jonathan Hutchinson's case.)

traced as thickened solid cords through the cardiac tissue. The thyroid was normal; the splenic capsule was immensely thickened on its convex surface; the kidneys fibrous (senile); the supra-renal capsules shrivelled; the stomach and intestines so atrophied as to be almost transparent, resembling wet paper. The liver was relatively large; the brain normal, in



FIG. 56.—*Progeria*. Case 2.—Aged 16 years. Compare with a normal hand. The fingers are especially short, and the unequal phalanges are shapeless nobs. The size of the hand is equal to that of a normal child of three, but the ossification corresponds with that which is usual at twenty. The knuckles are big in comparison with the shafts of the long bones. (Sir Jonathan Hutchinson's case.)

keeping with his intelligence, which had been good. The tonsils and Peyer's patches were wasted. The long bones were, as a rule, small and delicately formed, but were relatively large at their ends, especially those

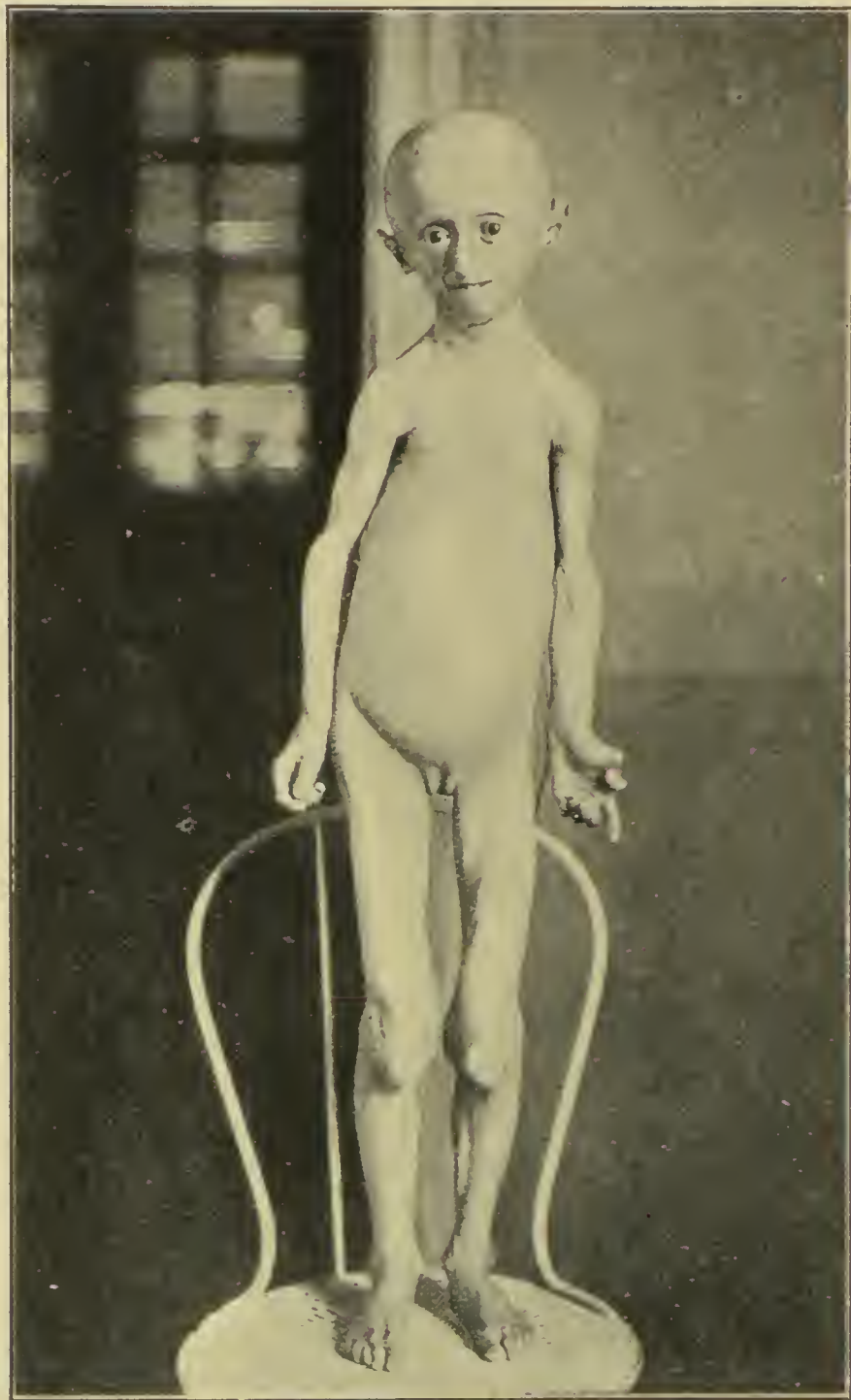


FIG. 57.—*Progeria*. Portrait given by Dr. Variot, and reproduced with his permission. (Dr. Variot's case.)

about the knee-joints, those of the long bones of the hands and feet, and the sternal ends of the clavicles. Their ossification was, generally speaking, a little premature.

CASE 2.—This lad died at the age of seventeen from symptoms suggestive of cardiac syncope. He was known to have disease of the mitral and aortic valves, but no *post-mortem* examination was permitted. In all essential respects he closely resembled the previous case.

The features of these two cases may be summed up as a remarkable mixture of infantilism with senilism, mingled with indications of a more ordinary development.

CASE 3.—This case of MM. Variot and Pironneau* is that of a girl, aged 15 years, in whom the disease began without apparent cause when she was about eighteen months old, just after weaning. A photograph taken when the child was one year old showed a perfectly normal, fattish child: but two portraits of the same girl at the age of fifteen years were significant of a remarkable transformation in the interval. The resemblance to the first two cases is exceedingly close, as will be evident upon comparing the pictures. Though of the height (102 cm.) usual at five years, the emaciation was so great that her weight (11.65 kg.) was not more than that of a child of two years, and the circumference of her cranium (47.5 cm.) was of the seventeen months' standard. The nose was of the same aquiline stamp, and its cartilages were as prominent as in the other cases. No hair could be found anywhere. A picture of a radiogram of the hand and wrist closely corresponds with that which we give of the similar parts of Case 2, except that the former shows a malformation of the thumb. In short, in every important particular the characters are almost identical with those of the other two cases. Dr. Variot is inclined to attribute the disorder to disease of the supra-renal capsules, and recorded the case under the title of "Nanisme avec dystrophie osseuse et cutanée spéciales: soupçon d'agénésie des capsules surrenales."

Pathology of Progeria.

The pathology of progeria is to a large extent dependent upon the reply to the question, Is it secondary to the disorder of some particular organ, or is it a primary affection of the body as a whole?

The answer must be that at the autopsy on Case 2 the thyroid gland, pituitary body, brain, testes, and supra-renal capsules were all examined, and it did not seem possible to accuse any of them of being responsible for the general disturbance. But the organ which ought to have been examined with the greatest care was, we regret to say, passed over with a very casual inspection. This was the pituitary body. This seemed to the naked eye to be quite healthy,

* 'Bull. de la Soc. de Pédiat. de Paris,' June, 1910, p. 307; see also a later paper in 'La Clinique Infantile,' vol. viii, 1910, p. 705.

but had we known the importance this organ was afterwards to assume, we should certainly have examined it more minutely. Dr. Woods Hutchinson,* basing his opinion upon embryonic and pathological and morphological grounds, is of opinion that the pituitary body is a "growth centre."

He points to acromegaly and gigantism in corroboration of the view, and mentions that he has examined the pituitary body of a dwarf and that it was diseased. He found that in gigantism there is hypertrophy of the glandular portion of the hypophysis, whereas in the case of dwarfism this part had undergone atrophy. It may be remembered that Paltan†'s case‡ of ateleiosis was noticed to have enlargement of the pituitary body, but nothing is said of the nature of the enlargement. In view of the fact that no special attention seems to have been directed to this organ in any other case, and that it might be seriously diseased without being affected in size, it cannot be said that this negative evidence is of any real value.

The characters opposed to those which are found in acromegaly were the facts that they were dwarfs, not giants: had thin lips, small tongues, and ill-developed mandibles, instead of the thick lips, big tongues, and huge lower jaws of acromegaly. Moreover, the collar-bone was diminutive, and the skin with its appendages atrophied, whereas in some cases of acromegaly the collar-bone is too big, and the skin is voluminous, so that it may hang in folds.

But there seem to be insuperable objections to regarding progeria as dependent upon disease of the pituitary body. Indeed, the very circumstance that the symptoms suggestive of pituitary disorder are capable of being placed in contradictory groups is by itself enough to indicate that we must go elsewhere for an explanation.†

The facts, to our thinking, point to the conclusion that progeria is a premature senile decay, affecting the body as a whole, arising in an individual in a state of infantilism, and manifesting itself, as is usual with senility, in some organs more than in others. The reasons for this opinion are based partly upon what has already been said in this book on the subject of senilism in general and its relations to infantilism, and partly upon a further consideration of the disease acromegaly, such as will be gone into presently when we come to deal with that subject.

* "The Pituitary Gland as a Factor in Acromegaly and Giantism," 'New York Med. Journ.,' vol. lxxvii, 1898, pp. 341 and 350, and vol. lxxii, 1900, pp. 89 and 133.

† 'Ueber den Zwergwuchs in Anat. u. Gerichtsärztlicher, Beziehung,' 1891.

‡ Dr. Variot ('La Clinique Infantile,' 8 année December, 1910, p. 105) thinks that there is good reason to regard the suprarenal bodies as the source of the malady.

Progeria Beginning at the Age of Eight or Nine.

On the occasion of the introduction of the records of the first two cases of progeria before the Royal Medico-Chirurgical Society in 1897 a portrait of a possible third case was also produced. But it must be confessed the evidences of the disease were of the slightest, and those present at the meeting who passed an opinion on the subject could see nothing abnormal in the photograph.

This opinion, coming, as it did, from those whose experience and judgment in these questions of diagnosis was vastly superior to our own, was decisive. No further thought was given to the case, so that in course of time it had faded from the memory until one day thirteen years after the portrait was taken. The whole incident was then forcibly recalled to our recollection by the sudden appearance in the consulting room of a little, meagre individual of insignificant presence who was immediately recognised as the boy we had once seen and photographed when of the age of nine. He was now twenty-two years old, but in the interval the scanty signs of mixed immaturity and prematurity which had first attracted attention had so increased as to be obvious at a glance. The lapse of years had accentuated both the prematurity and the infantilism. We regret to say that the pleasure of seeing our diagnosis apparently verified for the time being completely overcame any feeling of commiseration for the unfortunate patient.

The *infantilism* was pretty conspicuous in his height, which was 118 cm., and in his weight (41.2 kg.), which would therefore correspond with those normal to a boy of 13½ years.

His sex development was about equal to that customary at fifteen or sixteen. There was a scanty crop of feeble hair on the chin and in the region of the whiskers, and a more plentiful but inadequate supply on the mons martis and in the axillæ.

Premature regressive development was indicated by his aspect and bearing, which were those of a man of past thirty. His face was thin, and slightly wizened, so that it readily wrinkled when he moved his features in talking or smiling. The nose was prominent and its cartilages conspicuous, the lower jaw small, and the ear lobules defective.

He was of poor physique and could not stand hard work, so that his record since he started in life was one of successive failures owing to bad health. His various occupations had included jockeying, stone-picking, odd jobbing, light gardening. As a jockey he broke down as the result of a syncopeal attack, weakness with aching of the loins stopped his stone-picking, and some chest trouble (pneumonic?) put an end to some other

occupation. His muscular power was weak. His intelligence was fair, and the circumference of his head was 55·8 cm. It seems that his parents and



FIG. 58.—*Progeria*. The disorder began in late childhood. He is now aged 22 years, and is of the size and weight usual at fourteen. Infantilism is mingled with senilism, but neither is very conspicuous. The picture does not do justice to the aged appearance of the face.

four brothers and sisters are all of normal height and appearance and that he is singular in his stature, physiognomy, and physique. He is quite

unable to account for his condition, for he was normal as a child, and did not begin to change until he was about nine years old.

Remarks.—The notable features, and those which identify this case with progeria, are the blend of infantilism with a too forward regressive development (senilism), and the facts that the abnormality began without apparent cause in a member of a normal family. Moreover, the condition cannot be accounted for on any other grounds.

At the same time it must be admitted that the indications of progeria are very inconspicuous in comparison with those in the three cases which have been recorded. But this is satisfactorily to be accounted for by the fact that this last case occurred at a time of life when the body had already made some considerable headway towards maturity. Hence the infantilism was much less obvious, and as for the senilism, we have already seen that the onset of premature old age becomes less and less pathological the older the patient, the more nearly the construction of the body is completed.

Doubtful Cases.

The nearest approach we have been able to find to the cases which have just been described is the following, but unfortunately the details given are not sufficient to justify us in definitely classifying it under the same heading.

In 1751 Mr. Baker read a letter to the Royal Society, which he had received from Mr. John Browning, a surgeon, concerning a dwarf. It was accompanied by a certificate signed by "eight gentlemen of figure and fortune," signifying that the particulars there given were correct. His name was Hopkin Hopkins. The father and mother were of ordinary stature and had six children, of whom Hopkin was the second.

Mr. Browning says in his letter: "His stature is not more than 2 ft. 7 in. (80 cm.), and weight 13 lb. (5·8 kg.); labouring under all the miseries and calamities of very old age, being weak and emaciated, his eyes dim, his hearing very bad, his countenance fallen, his voice very low and hollow, a dry, husky cough, low and hollow; his head hanging down before, so that his chin touches his dress; consequently his shoulders are raised and his back rounded, not unlike a hump-back; his teeth are all decayed and rotten, except one front tooth below; he is so weak that he cannot stand erect without a support.

"His father and mother both tell me that he was naturally

sprightly, though weakly, until he was seven years old, without attempting to sing or play, and then weighed 19 lb. (8·6 kg.), and was as tall as, if not taller, than at present—naturally straight, well-grown, and in due proportion; but from that period he gradually declined and grew weaker, losing his teeth by degrees, and is now reduced to the unhappy state I have described. The mother is a very jolly, healthy woman, in the prime of life, the father enjoys the same blessing; they both assure me that this lad has a sister about ten years of age in the same declining state.”

In a notice of his death, which was inserted in the ‘Gentleman’s Magazine,’* it is stated that his sister of “twelve years old weighed only 8 lb. (3·6 kg.), and bears upon her most of the marks of old age, and in all respects resembles her brother at that age.”

The characters in this case, causing it to stand out so conspicuously from the general level of normal development, and the complete absence of motive, are sufficient, even in the absence of heredity, to mark it as a *major or discontinuous variation*. Moreover it is a variation, apparently not of any one particular organ, but of the body as a whole.

One of the most extraordinary instances of male prococity that we have had brought to our notice was contained in some newspaper slips which were recently sent from America. The following is a copy of that which was cut from the ‘New York Herald’ of August 21st, 1896.

“CHILD DIES OF OLD AGE.

“*Case of Senile Debility in an Infant whose Brain showed Signs of Growth almost at Birth.*

“ [BY TELEGRAPH TO THE ‘HERALD.’]

“ST. LOUIS, Mo., August 20th, 1896.—A remarkable phenomenon in the person of a child eight months old, which died of senile debility, was discovered in this city. The child, Herman Robert Burch, first came under the observation of Dr. Edward Randall two weeks ago, when it was brought to the North Side Dispensary for treatment by its mother.

“It was a monstrosity. Its body had ceased to grow after birth, but the head was fully developed, the face bearing all the marks of an old man. The head was covered with coarse hair, and on the face was a straggling beard (moustache).

“The child was born last December, and on Monday it died of

* Vol. xxiv, 1754, p. 191.

old age. It had passed through all the intellectual phases that are common to mankind, but so rapidly that it had not the time to



FIG. 59.

gather the knowledge that comes of experience and precept, or the wisdom born of thought.

“ ‘The baby was unusually bright,’ said the mother. ‘He began to notice almost as soon as he was born, and seemed to know

as much as his elder brother, who was a year old. He never did look like a child or act like one.'”*

The picture was copied from ‘The World,’ one of the principal newspapers of the city in which this sensational account originated. It will be observed that the head is unduly large for the body; the arm and hand are thin and delicate; the hair is abundant for one so young; there is hair on the upper lip, which hair the artist has evidently exaggerated into a fairly conspicuous moustache; the face is lean; the eyes are big and staring. The nose is large and aquiline, and the lips are thin. The lower jaw is deep, and the angle small, pointing to an advanced state of ossification.

II. Consecutive Senilism.

It has been noticed that those who are affected with ateleiosis, though retaining the configuration of childhood, are prone to become prematurely wrinkled and aged looking. Thus photographs of the case described on p. 603 taken two years later, when he was twenty-eight years of age, show that in the interval he had become decidedly more senile in appearance. In fact, so far as externals were concerned he looked nearer forty than thirty. So, also, in Dr. Parkes Weber’s case (p. 608) the corrugated skin of the face and the wrinkled and wizened appearance of the whole body, as shown in the excellent portraits which go with the article, are suggestive of an older individual.

In the following case this appearance of premature age came on much earlier and was far more pronounced. So much was this the case that we were at first inclined to regard him as an example of progeria, but the relatives still living are positive that the appearance of old age did not begin until some ten or twelve years before death. The facts about to be given, together with the photograph, were told us by the late Dr. Bateman, of Whitechurch.

* Since this was written we have received a letter from Dr. Randall, of St. Louis, in which he says: “The story given in the newspaper was not exaggerated. The child had the appearance, as far as the facial expression was concerned, of an old insane man about sixty to seventy years of age. It had slight moustaches, the bones of the head were ossified as in mature age, and the anterior and posterior fontanelles were closed as solidly as in old age, the only difference being that they had ossified slightly below the remainder of the skull. The lower portions of the body were not apparently developed at all below the neck. An autopsy was held by me, showing the brain to be in an advanced state of development, and all the bones of the head as above stated. It died with all the symptoms of senile debility when it was but eight months of age. The newspapers have a good likeness of it sketched by an artist. It is the only one taken, and is very expressive.”



FIG. 60.—*Consecutive senilism; premature old age apparently secondary to ateleiosis.*—The patient is of childish size and proportions, but died two years after the portrait was taken from senile decay, aged 42 years. Compare with the portrait of a case of progeria on p. 649. The face is broader and flatter; the nose less prominent; the chin projecting. Except for the appearance of age, the features are more like those of ateleiosis (fig. 27) than of progeria.

The patient, S. K—, was a single woman. Her parents were of ordinary stature, but she had two brothers who resembled herself in size and appearance, one of whom died from intestinal obstruction when about twenty-one years of age, and the other from some affection of the lungs. A brother and sister of normal development are still alive.

Towards the close of her life S. K— became old-looking and decrepit. She was about 124 cm. in height, was not deformed, but was thin, so that the superficial veins and tendons showed very conspicuously. The skin was loose, wrinkled, dry and shrivelled. The hair of the head was grey, and very sparse indeed, so that the skin could be everywhere seen without interfering with the hair. The nails, also, were thin and ill-formed. Her muscles were of very poor development, and the joints seemed very prominent, but Dr. Bateman could not say whether this was due to their enlargement or to shrinkage of the soft parts around them. The eyes seemed to be unusually large and prominent. The nose was neither snubbed nor aquiline, and the cartilages were not conspicuous. The intelligence was good. There appeared to be no disease of any organ, but no special examination was made of the heart or of the urine. There was no indication of syphilis or rickets. Though never actually ill, she was too weak and frail to be capable of doing any prolonged work. Finally, she presented such a striking picture of advanced and benignant old age that some of the "gentry" of her neighbourhood, who were much interested in her, took her into Reading to be photographed. This portrait was taken when she was forty years of age, and she died two years afterwards, apparently from senile decay. She became gradually weaker, then bedridden and childish, and finally died suddenly after the manner of old people.

Senilism secondary to Infantilism associated with Defective Development of the Sexual Organs and with Diabetes.

An interesting case is described by Dr. Ransom. It is that of a girl, aged 27 years, 4 ft. 3½ in. (135 cm.) high, and weighing 35½ lb. (16 kg.), whose father was a drunken "degenerate."

She herself was of defective intelligence, and at school could not get beyond Standard III. She had been subject to diarrhœa all her life until symptoms of diabetes appeared.

Infantilism was shown in her height (equal to that usual at ten years), mental condition and facial proportions (resembling that of a girl of eleven or twelve), but above all in her sexual characters.

These in respect to outward appearance were said to be like those of a girl of ten, but after death the uterus was found to be almost absent; there were no ovaries, and the internal sexual organs consisted of no more than two big Fallopian tubes a little thickened at their point of junction.

Senilism was shown in the attitude, in the emaciation, and in the atrophy of the buttocks. The face was "pinched and worn, and with a suggestion of age in it." Senile (fibrotic) changes were also present in the spleen, lymph-glands, pancreas, kidneys, supra-renal bodies, thyroid gland, pituitary body and bone (rib). The heart weighed 6 oz., and there were "some atheromatous patches on the aortic and mitral valves and on the aorta."

Other anomalies were present in the shape of an enlarged clitoris and diabetes.

The case is one of great interest, and serves to illustrate the difficulty that must sometimes arise in determining whether a particular disease of development be a major or minor variation. Possibly both kinds of variation were present in this case. The general infantilism seems to have been of the minor order, for there is nothing characteristic in the physiognomy, the defect of general development was not conspicuously striking, and the defect of intelligence as well as the diarrhœa are highly suggestive of Lorain's type of induced infantilism, either pancreatic or intestinal. At the same time the combination of so many disorders in one individual is more in favour of their being of major than of minor degree.

The remarkable disease, of which a case has been recorded by MM. A. Souquès and J. B. Charcot,* and by them named "*Giromorphisme cutané*," at first sight suggests a relation to progeria. But in reality the resemblance is only superficial, for the written particulars and the pictures both tend to show that the senilism is of the skin only. It is to all appearances a disease of the skin as an organ and not of the whole body.

* 'Nouvelle Iconographie de la Salpêtrière,' t. iv, 1891, p. 169.

VI

GENERAL SENILISM AS A MAJOR VARIATION—CONTINUED; PRIMARY SENILISM: ACROMEGALY *

Acromegaly is characterised by the reappearance of the features of paleolithic man.

These are similar in kind, though greater in degree, to those which appear in normal old age. In acromegaly, as in normal old age, there is a generalised failure of developmental control leading to irregularities of growth, especially of those parts in which function and structure have reached their highest perfection. In acromegaly this impairment is carried to a pathological extreme, and is shown in manifest enlargement of the extremities and organs, among them being the hands, feet, nose, tongue, jaw and internal organs, including the pituitary body.

It is peculiarly fitting that this disease should come at the end of a work on post-natal growth and development in their morbid aspects, for it seems in itself to contain the elements and to furnish an illustration of the principles of these disorders as they affect the different parts of the body, separate or combined.

But before entering upon this subject we must premise that we have in truth to deal with a disorder that comes within our province. We must first show that it answers to the tests requisite for a disorder of growth or development, and is indeed a variation.

Dr. George Dock, in his admirable article in Osler and McCrae's 'System of Medicine' (p. 463), in giving a summary of *causes* of acromegaly, states that the assigned causes are "alcohol, lead, syphilis, emotional shock, such as fright, various infectious diseases, typhoid and scarlet fever, poisoning by illuminating gas, and trauma." Though it is true, as he and others have pointed out, that in many cases the cause assigned is not the real origin of the disease, yet it is conceivable that some member of this group of agents is capable of starting acromegaly on its way, or of acting as an impelling force when it has already started. In such circumstances the disease is a *minor variation*.

But in most cases no cause can be found. At the same time it

* The material for this chapter was taken for the most part from the New Sydenham Society's translations of the works of Marie, Souza-Leite, and of Sternberg.

is very unusual to find evidences of direct *heredity*. This, no doubt, is partly because acromegaly is a sterilising disease, and effectually stands in the way of its own transmission. Yet hereditary influences seem to be present in some cases, for Byrom Brainwell reports two cases of familial heredity, and Sternberg two probable cases. Moreover, apparent examples of *transforming heredity* are fairly common. Thus Mr. Gordon Brown* published an instance in which the father of a patient with acromegaly died from pernicious anaemia, and the mother was epileptic. "Inherited nervous disease" is a frequent family precursor, and so is diabetes. Goitre also is often mentioned, and Drs. Pope and Clarke† write of the occurrence of acromegaly in a man who, some fourteen years before the appearance of his disease, became the father of a girl, who, at the age of five, was affected with myxœdema. In another case, given by C. K. Mills,‡ the mother was feeble-minded, and the father a chronic alcoholic. Of course the presence of the diseases in the same family may have been a mere coincidence, but this becomes highly improbable when the associated diseases are of rare occurrence.

Among the diseases which are *associated* with acromegaly in the same individual are goitre, pre-natal stenosis of the aorta (one case), genital aplasia (three cases); moreover, it may be suspected that some of the diseases which apparently spring up as part of the acromegaly are in reality merely associated conditions. Among these are goitre, diabetes, epilepsy, syringomyelia, hyperostosis. Thus, Lancereaux reports a case in which acromegaly co-existed with diabetes and with exophthalmic goitre, and the father was diabetic. Cases of this kind serve to show how impossible it is in such a disorder as acromegaly to separate consequential from associated diseases.

Enough has been said to show that acromegaly exists as a *major variation*. Possibly all cases of acromegaly are of this nature, and what are thought to be causes are not so in reality.

The *course* of the disease is variable. It is notoriously subject to spontaneous exacerbations and remissions. These remissions may last for months or years, and give rise to much perplexity in regard both to prognosis and to treatment.

No medicinal treatment is of any lasting use, though Dr. Campbell and others have found *arsenic* of service. The only hope at present

* 'Brit. Med. Journ.,' 1892, vol. i, p. 862.

† *Ibid.*, 1903, vol. ii, p. 1563.

‡ 'Diseases of Children,' Starr, vol. ii, p. 691.

is in surgery, which may be depended upon to relieve headache and other pressure symptoms.

The *pathology* of acromegaly is one of the enigmas of medicine. Most authorities regard it as the outcome of disease of the pituitary body, but those who pin their faith to this hypothesis encounter many difficulties. Thus, for example, an organ so small in size, capable of producing such widespread and important effects, must, under normal circumstances, possess highly important properties. In fact, if we may judge from the results of its disease in acromegaly, we have concentrated in one small organ as great a potency as is collected in the whole of the thyroid gland. It is usual to regard acromegaly as having the same relation to disorder of the pituitary body that adult myxœdema has to disorder of the thyroid gland. But it is almost out of the question that the pituitary body should be affected always in the same way, or give rise to only one set of symptoms. It must, like every other organ in the body, be subject to the extremes of growth and of development, each expressing itself by some characteristic array of symptoms. There must be such a condition as absence or hypoplasia of the hypophysis. But, if so, it seems incredible that serious defect of such a highly important organ should give rise to no symptoms. Yet if acromegaly correspond with myxœdema, what disease corresponds with cretinism?

Overgrowth, again, of the thyroid gland presents us with one of the most striking maladies to which the body is subject, to wit, Graves's disease. No greater contrast can be imagined than that between the dull, cold, heavy torpidity of myxœdema, and the hypersensitiveness, the emaciation, and the tremulous cachexia of Graves's disease. Yet no one has described any morbid state which is to acromegaly what Graves's disease is to myxœdema.

Indeed, it cannot as yet be said that we are acquainted with the somewhat elementary knowledge of the exact morbid state of the pituitary body in acromegaly. Reports on this head vary extremely. In some autopsies it is described as in a state of simple hypertrophy, in others of atrophy, and in yet others of fibrosis; sometimes adenomata or cysts are found, and sometimes carcinomata or sarcomata. In short, in different cases we can run through the whole gamut of hyperplasias and degenerations. Though acromegaly is by some attributed to the work of degeneration or destructive processes, the tendency in our days is to regard it as the result of overgrowth with hypersecretion (Souza-Leite, Benda, Bassoe,* Woods Hutchinson). It seems highly probable that the pituitary

* 'Journ. of Nerv. and Ment. Dis.,' vol. xxx, 1903, pp. 513 and 595.

body behaves, under the influence of disease, much in the same way as the thyroid gland, or, indeed, any other organ in the body. In other words, it is liable to hyperplasia, and this hyperplasia is prone to degenerate (degenerative hyperplasia), and when in this state is apt to degenerate further and to become the seat of such single cell overgrowths as the adenomata, or to the single cell degenerations of cancer. In other cases fibrous, or cystic, or cancerous degeneration takes place in an organ of defective development, or even in a normally formed organ.

Though it is the fashion nowadays to regard acromegaly as the result of simple hyperplasia, yet this does not seem very consistent with the facts that with some conspicuous exceptions the disease is obviously more akin to myxœdema than to Graves's disease, and that the most rapid and pronounced cases of acromegaly are those in which there is most destruction, usually cancerous. Another discrepancy, difficult to account for under the pituitary hypothesis, is that no less than fifty cases have been reported in which the pituitary body has been found to be the seat of disease, though no acromegaly existed. Yet in many of these cases the morbid condition of the organ has seemed in no respect to differ from that which is found in acromegaly. In yet other cases the sella turcica, or the gland itself, is found not to be enlarged, though it is said that in such cases minute examination invariably reveals some indication of disease. Thus in Linsmeyer's case there was a softening adenoma within the gland. In two cases, referred to by Tamburini,* in which there were no naked-eye appearances of disease, the acromegaly was only about six months old, and no microscope examination was made. In Dr. Saundby's case† the disease began only five months before death. There was no enlargement of the jaws, and the patient had spindle-celled sarcoma of the lungs. This case was included by Souza-Leite among his cases of acromegaly. A microscope examination was made of the thyroid gland, which was found degenerated, but not of the pituitary body, because of its normal appearance. Is it possible that this was a case of pulmonary osteoarthropathy?

Dr. Lewis,‡ on making a microscopic examination of a pituitary body from a case of acromegaly, without macroscopic appearance of disease, found an increase of chromophile cells and a loss of chromophobe.

* 'Riv. Sperimentale di freniatria,' vol. xxi, 1895, p. 414.

† 'Illustrated Med. News,' 1889, vol. ii, p. 196.

‡ 'Johns Hopkins Hosp. Bull.,' vol. xvi, 1905, p. 157.

It must be obvious that much of the evidence which is brought forward in favour of the pituitary origin of acromegaly is very weak and inconclusive, if not positively contradictory. Whereas we should anticipate that a gland of such extraordinary potency as is implied in acromegaly would furnish us with not one but with a whole group of diseases, each one not only pronounced in itself, but obviously distinct from the others, yet this is by no means the case, for we know of only one malady which can, with any show of evidence, be attributed to disease of the pituitary organ, and that is acromegaly.

Let us now take a comprehensive review of the chief, outstanding features of acromegaly. We notice, in the first place, the extraordinary variety of its symptoms. These symptoms are, however, capable of being segregated into three groups.

Some of the symptoms (*e. g.* headache, vomiting, apathy, impairment of vision) may obviously be attributed to pressure of the pituitary tumour within the cranium. Others, which can be produced by removal of the pituitary body in lower mammals, may be the direct, specific result of interference with the action of the pituitary organ. Drs. Crowe, Cushing, and Homans,* in an important paper giving the results of removal of the pituitary body from dogs, conclude that hypopituitarism induces adiposity, as well as polyuria, glycosuria, nutritional changes in the skin and its appendages, and certain psychical disturbances, with either drowsiness, or with restless playfulness. The sexual glands of young animals remain undeveloped, and those of older animals degenerate. Still more interesting is the conclusion that pituitary deficiency does not lead to gigantism, but to defective growth, or infantilism.

But even when we put on one side all the above symptoms, due either to pressure of the pituitary tumour, or to its defective action, a great number are still not accounted for.

The lesions of acromegaly differ, moreover, not only in situation but in kind. *Hypoplasia* of the thyroid, of the aortic orifice of the heart, of the red blood discs, of the muscles, are all mentioned; so are *overgrowth* of the brain, thyroid, thymus, eyes, hair, skin, bones, lymph-glands, spleen, tonsils, heart, blood-vessels, leucocytes, erythrocytes, the external genitals or muscles. In other cases excessive hunger or excessive thirst exist without diabetes; or there is obesity. Profuse perspiration, galactorrhœa, also occur. In yet other cases we meet with *degeneration* of the brain, thyroid, joints, muscles, spinal cord, kidneys, liver, arteries. Moreover,

* 'Johns Hopkins Hosp. Bull.,' vol. xxi, 1910, p. 127.

not only organs but the constituent tissues of the body are liable to similar disturbances, so that we have outgrowths of bone, cartilage, gland-tissue (adenomata), as well as the different sorts of cancer. Sometimes these various excesses of organ or tissue are so numerous that we have a condition of splanchnomegaly, in which nearly all the viscera are affected, as well as the external organs.

We have seen one case of acromegaly which presented unusual features.

It was that of a youth, aged 19 years, who showed evidences of acromegaly to a fairly conspicuous degree. He was over 198 cm. high, and was thin and gaunt, knock-kneed, and loosely knit. His hands and feet were so large that the stock sizes of gloves and boots were too small for him. His eyebrows were prominent and lower jaw large and projecting, so that the upper incisor teeth rode behind the lower.

But the peculiarity of his case consisted in his extraordinary gift of tongues. He was familiar with Spanish, German, French, and English, and claimed acquaintance with three other modern languages. We were able to test his veracity with regard to three of these languages, and found no reason to doubt his word. Though an accomplished linguist, his mental state, as a whole, was as loose and disjointed as his physical. He was accustomed to keep a note-book, in which he jotted down memoranda of striking events. This contained many foolish or whimsical conceits, and, together with his conversation, served to show that his intelligence was in some respects little better than that of a child. He had acted as interpreter in South Africa and again in London, but his occupation had been so often interrupted by bouts of bad health that at last he could get no regular work, and at the time we saw him was looking unkempt and shabbily clothed, and was walking from town to town as a tramp.

Of all the organs perhaps the one most consistently deranged—more often, indeed, than the hypophysis itself—is the skeleton. The hands and feet, the nose, the lower jaw, and the supra-orbital prominences are most conspicuously enlarged, and often the bones, and especially the skull bones, are eminently suggestive of, or even indistinguishable from, osteitis deformans,* or the marrow is so increased in quantity and affected in quality as to remind one of that of osteomalacia (Boltz).

This is not all. Not only organs and cells, but the body as a whole is liable to derangement of growth and development. There is general weakness, the back becomes bowed, the knees bent, the attitude feeble,

* Shattock, 'Path. Soc. Trans., Lond.,' vol. 1, 1899, p. 186; Broca, 'Archiv. général de Méd.,' vol. ii, 1888, p. 656.

and the gait tottering, so that the acromegalic, like the old man, has to depend upon the help of a stick.



FIG. 61.—Giant Winkelmeyer (2.28 m. in height). The size of the feet and hands, the projection of the lower jaw and the fulness of the supraorbital region are indicative of acromegaly. The skeleton has apparently gone ahead of the soft parts in its growth, for the correlation between them is very imperfect. From a photograph by the London Stereoscopic Co.

In some cases it is stated that women affected with acromegaly have grown facial hair, and have given evidences in other ways of possessing masculine traits (Hutchinson), and *vice-versâ*, men sometimes show indications of feminism. Some cases are recorded of delayed ossification, as well as of other indications of general infantilism. But these cases are by no means so common as those which show evidences of senilism. Indeed, so invariably is this last that it can safely be said that there are no cases of advanced acromegaly in which these senile changes do not form a conspicuous feature.

Evidences of senilism.—Attention has already been drawn in the first part of this book to some of those characters of senile decay which are of a reversionary nature. The bent back, yielding lower limbs, sunken head, overhanging eyebrows of many old men are distinctly simian, and so are the growth of hair over the body, and the defect of muscle control, as shown in clumsiness of movement.

All these characters occur in an exaggerated degree in acromegaly.

Let us now turn on one side, and ask what is the meaning of these simian characters in old age.

If we regard one of the higher apes of mature age we see that, compared with man, his size is gigantic.* At the same time his back is so curved, his head so sunken, and his lower limbs so bent, that we do not perceive his height, but detect only his enormous breadth and his huge display of muscles. He is very loosely put together, and is compact of bone and muscle, so arranged that, compared with man, his proportions are displeasing and ungraceful. The hands and feet are too big, the forearms too long, the attitude weak, the balance uncertain. All these imperfections are intensified in the face, which is obtrusive, coarsely moulded, and destitute of refinement. Indeed, owing mainly to the irregularity of their disposition, the features of the full-grown chimpanzee or gorilla are revoltingly ugly. A ferocious and sinister cast is given by the projection of the eye-brows, which confers a perpetual scowl, heightened, if possible, by the brutish projection of the jaws, especially the lower.

At the same time it is probably a mistake to infer, as we are all apt to do, that the disposition and actions of these anthropoid apes is invariably in keeping with our interpretation of their appearance. The formidable-looking adult orang as described by Wallace, or the chimpanzee or gorilla as described by Du Chaillu, is no doubt a terrifying object when provoked, but there is no reason to suppose

* A gorilla shot by Herr Paschen measured 206 cm. in height (crown of head to tip of middle toe). Its skin and skull are now in Lord Rothschild's museum at Tring.

that in his normal state, among his own kin, these aggressive characters are often displayed. Probably the manners of these apes when among themselves are amiable enough. Though capable, like man himself, of ferocity, their facial characters are not the result of lives spent in a turmoil of evil passions, but are simply an indication that they have not yet arrived at a stage of evolution which admits the display of the finer emotions and of character in the countenance. Compared with man they are as yet defective, both in regard to bodily and to mental endowment. In other words,



FIG. 62.—AGED 24 YEARS. NORMAL APPEARANCE.

they are admirably fitted for the rough life of the forest in which they live.

Simian characters of acromegaly.—While ape-like characters are clearly enough to be detected in old age, in acromegaly they stand out so prominently as, indeed, veritably to constitute the disease itself. In fact, they have arrested attention from the beginning, and were even remarked by some observers before Marie had defined and named the disease. Thus, Freund, in 1872, or thirteen years before Marie's essay, noted that a young woman of sixteen, affected with what was afterwards known to be acromegaly,

was so simian in appearance that he “almost fancied that he had before him a kind of anthropoid ape, clothed in human dress and walking like a man” (Souza-Leite). Brigidi (1877), in describing the *post-mortem* examination of a patient who had died of the same disease, “brought into prominence the resemblance of the skeleton to that of an orang outang,” Cunningham (1878) “was particularly struck with the appearance of the patient, which he compared with that of a gorilla,” and Brissaud, Meige, and Woods Hutchin-



FIG. 63.—AGED 38 YEARS.

FIGS. 62 AND 63.—*Acromegaly*. In the second figure the facial characters have undergone very conspicuous alteration. The nose has become big and shapeless, the eyebrows a little fuller, the lips thick, the ear large, the lower jaw more projecting: the back also is curved, and the hands are large and podgy. All these are simian features, and represent the changes of age taking place to an exaggerated degree. The woman looks nearer sixty than thirty-eight. (Mr. Ruttle's case.)*

son have noticed a similar likeness. Campbell (1894) has also commented on the striking resemblance of the features of acromegaly to those of anthropoid apes. Indeed, he and Frennd are responsible for the theory that the disease is nothing more than a reversion.

* ‘Brit. Med. Journ.,’ 1891, vol. i. p. 697.

This view of Freund and of Campbell is that which we are forced to adopt as the logical conclusion of what has now been stated. It brings us back to the point from which we started, namely, that acromegaly both in its structural and in its clinical features, presents all the evidences necessary for a retrogressive variation or reversion.

Let us once more go back to the old man and to the anthropoid ape, and see in what way the simian characters of acromegaly are brought about.

We notice that after the period of childhood has gone by the developmental progress of a higher ape is, so to speak, a retrograde progress. The young gorilla or chimpanzee is a remarkably human beast. He has a large domed head and comparatively small face, and is correspondingly intelligent, so that he is an attractive little animal, and displays wonderful capacity for adaptation to human manners and customs. Moreover, his bodily conformation is decidedly more after the human model than is the case later on. But as he grows older his intelligence leaves him; his face becomes larger and coarser, while his brain remains stationary, so that at maturity many of his anthropoid characters have gone, and his brutish predominate. This progressive deterioration is, of course, but the repetition of his racial descent. He comes from a degenerating stock, and therefore himself degenerates.

In the case of the old man a similar degradation is in progress, though it begins much later in life, and is the expression, not of a long line of degenerate ancestry, but of the deterioration of the individual. Hence it will be noticed that both in the ape and in the man we arrive at a similar result though in a different way.

In acromegaly simian characters arise in yet a third way. They are not due to the recapitulation of a degenerate ancestry, nor are they the result of normal senility, but are the outcome of variation carried to a pathological extreme. The bonds which hundreds of thousands of years of steady habit have imposed upon the course of development have become loosened, with the result that tissue growth tends to burst out in all directions, while development rushes on into prematurity. But necessarily those restraints which were last imposed are relaxed first, and the longer growth habits or developmental habits have been in existence the less likely are they to yield. It is after this fashion that we account for the irregularity of the changes in acromegaly, and for the way in which the overgrowth or the degeneration picks out the most highly developed, or most human, organs, especially the hands and feet, and that distinctively human organ, or series of organs, the expression-bearing face.

Among the organs so selected is the pituitary body, but why this organ should be so often and so seriously affected is not very evident.*



FIG. 64.—Australian man. The eyebrows are prominent and overhanging, the nose and ear big, the jaws projecting, the chin receding. The features in general are coarse and shapeless. Though sex hair is scanty the face as a whole is very hairy. From a photograph by Kerry & Co.

* That the enlargement of the hypophysis is not the prime factor in the situation, but is incidental, is held *inter alia* by Salberg, Dreschfeld, Bury, Hutchinson. Hutchinson, Bury and others have suggested that the enlargement is "part of the hypertrophy of the formation of the mouth, with which the hypophysis is connected during the process of development" (Sternberg).

Some of these simian features of acromegaly are eminently suggestive of a throw-back, if not to an anthropoid, at any rate to a very remote, stage of human evolution. The heavy, beetling eye-brows, which give such a sinister cast to the countenance of some old men, is very distinctly a relic of an older and more brutish stage of evolution. It is, no doubt, for this reason that the eye-brows are corrugated and made to overhang in the act of frowning, and that when the painter or sculptor desires to convey the impression of a brutish disposition, or the committal of an act of ferocity, he exaggerates the prominence of the eye-brows; and if he wish to emphasise this impression he takes care to endow his creation with a hunched back, a plentiful crop of shaggy hair, and a massive lower jaw, containing big teeth well exposed and firmly clenched. Indeed, in order to express anger in its more furious aspects it is evident that there can be no better way than to imitate the appearance and gestures of an ape.

The origin of the big nose of old age and of acromegaly is not so readily to be accounted for, seeing that the anthropoid apes are characterised by flat, inconspicuous noses. At the same time some of the lower species of monkeys have such very prominent noses as to constitute their most conspicuous feature. Moreover, when we go a little higher in the scale, we find that the skulls of early palæolithic man indicate that he possessed a very large and projecting nose, for the nasal bones and nasal processes of the upper maxillæ stood out in a way which admits of no other interpretation.* Indeed, the whole aspect of primitive palæolithic man, with his prominent supra-orbital ridges, large nose, heavy jaws, tall, thick-set, clumsy figure, stooping attitude and imperfectly developed intelligence must have been strikingly acromegalic.

Before we conclude it is necessary to say something more about the relations of acromegaly with gigantism. Any process which tends to the relaxation of the inhibitory forces of growth and development must necessarily vary in its effects with the age of its commencement. If it come into action before puberty, while growth is proceeding apace, it will tend to accelerate normal growth and development. If it be of lesser degree of severity it is conceivable that the hastening of these natural processes will be fairly uniform, and we shall have simple bodily overgrowth or moderate gigantism. But if more emphatic there will not only be gigantism, but the overgrowth will be more extreme, and at the same time

* Professor W. G. Sollas, "Palæolithic Races and their Modern Representatives," 'Science Progress,' No. 13, 1909, p. 16.

there will be a tendency for it to manifest itself more particularly in the terminal portions of the body, or organs, so that we shall have acromegalic gigantism. Between these forms, moreover, there will be all manner of gradations. An example of one of these intermediate forms is to be seen in the Museum of the Royal College of

EUROPEAN.

AUSTRALIAN.



PALEOLITHIC MAN.

APE.

FIG. 65.—Skulls showing apparent gradation from the anthropoid ape to the modern European.—2 was found in the department of the Corrèze. In 3 the frontal slope and the prognathism seem to be exaggerated by tilting. The capacity of the cranium increases from 1 to 4, the forehead becomes more vertical, the supra-orbital ridges less pronounced, the jaws not so heavy, and the teeth smaller and more regular. In 1 the chin is receding, the projection of the jaw being mainly alveolar, but as evolution advances the alveolar portion recedes and the chin projects. In 1 the bones are coarse and heavy, but become lighter and more delicate with each stage. Note the large size of the nasal orifice in 2. —Adapted from 'L'illustration,' Paris.

Surgeons. According to Mr. Shattock, the skeleton of Freeman (2 m.) is that of a "normal giant," because the pituitary fossa "is not in the least enlarged." Yet, at the same time, it is not altogether

free from indications of acromegaly; for, in addition to its excessive height, he "presents obvious prognathism," though Freeman was a white native of the United States. He also, as we have already observed (p. 488), showed indications of acromegaly in the coarse and mortary state of some of the bones.

A similar loss of inhibition taking place after puberty, when the growth forces of the body have expended themselves, can no longer result in universal giant growth, but in partial and scattered gigantism or acromegaly. Of this, too, there will be degrees according to the degree of inhibitory loss. Sternberg distinguishes three types, namely :

"(1) The benign form, up to fifty years' duration, and with trifling troubles.

"(2) The commonest form, chronic acromegaly, duration from eight to thirty years.

"(3) The acute, malignant form, of from three to four years' duration."

We have now seen that the body as a whole may be affected with simple hyperplasia, or overgrowth; and that this overgrowth, if moderate in degree, may become stationary, behaving, in fact, much in the same way as overgrowth of the brain and of some other organs. But often it runs on into a sort of degenerative hyperplasia, and ends in acromegaly, in a way which reminds us of the degenerative changes which are so apt to come upon overgrown organs.

It was stated a few pages back that if acromegaly be due to changes in the pituitary body, and correspond with myxœdema, there must be in existence a disease which is the result of hypoplasia, or defective development, of the pituitary body, in which we shall be able to detect qualities of the opposite nature to those met with in acromegaly.

But evidently the same line of argument must also apply if we regard acromegaly as fundamental, and the result of generalised loss of developmental control. In brief, if dwarfism be opposed to gigantism, and if acromegaly be regarded as senilism, it must necessarily follow that the fourth member of the group will be found in infantilism. Now it so happens that Woods Hutchinson, who has exhaustively studied the question of gigantism and acromegaly in all its bearings, has come to the conclusion that well-proportioned dwarfs of the infantile type (ateleiosis), possess characters which are of the opposite nature to those of acromegaly. At the same time, he is strongly of the opinion that all forms of gigantism and of acromegaly are due to primary disease of the pituitary body.

This being the case, he carries his hypothesis to its logical conclusion by supposing that these dwarfs, whom we regard as cases of infantilism, are affected with disease of the pituitary body of the opposite kind to that which gives rise to acromegaly. He believes that, whereas acromegaly is the result of hypertrophy of the hypophysis cerebri, dwarfism is the result of its defective development or absence. As a fact we are acquainted with one case in which the sella turcica was *enlarged* in a case of ateleiosis (see p. 602). But this seems to be the only instance of abnormality of this part among the few cases which have been examined. Yet, if Dr. Woods Hutchinson's inferences be correct, we ought confidently to expect evidences either of pituitary defect or of secondary degeneration in every case. But, though the facts do not support his views in regard to the predominance of the pituitary changes, the comparison which he draws between acromegaly and dwarfism (or what we term "senilism" and "infantilism") still holds good.

Dr. Woods Hutchinson* points out that whereas acromegaly tends to increase height and weight, to produce clumsiness of movement, sluggishness of intellect, undue preponderance of growth in the ends of the body, and premature old age, the dwarfism to which he refers is characterised by exactly opposite qualities. The height and weight are reduced, the body is constructed on better proportions and more gracefully, and the hands and feet, nose, lower jaw, and supra-orbital regions, are all of small size. Moreover, the general tendency of the disease is shown in the outward form of perpetual youth, and not in a grotesque exaggeration of the characters of old age.

It is right that we should now add our own endorsement of this opinion, though, as a matter of fact, this, so to say, preceded the statement by Dr. Woods Hutchinson which we wish to support. We have already alluded to this subject on p. 656 under the head of "Progeria." We need only add, that inasmuch as that disease seems to be a form of senilism consecutive to, or running side by side with, a state of infantilism, if what has just been said be correct, we should expect progeria to show changes of an opposite character to those of acromegaly, and mixed with them characters suggestive of acromegaly itself. Those who will turn to the original paper in the 'Medico-Chirurgical Transactions' of 1897 will see that these mixed characters were then pointed out and commented upon. They were, indeed, recognised long before their full significance was understood.

* 'New York Med. Journ.,' vol. lxxvii, 1898, pp. 341 and 350.

Moreover, in the cases referred to, the curious blend of the immature and the premature, of the comparatively big and the comparatively little, seemed to us to be the very essence of the disease, so that we suggested for it the provisional name of "micromegaly." We intended thereby not only to emphasize this combination of opposites, but also the relation with acromegaly.

We still think that micromegaly is a good descriptive word, despite its somewhat Hibernian flavour. But it sins against the canons of consistency and convention in disease nomenclature, and has therefore not been retained. Dr. George Dock, who agrees with Dr. Woods Hutchinson in the view he takes of the dominance of the pituitary body, believes that progeria will eventually be found to have its origin in some disorder of that organ. He therefore, in his article in Osler and McCrae's 'System,'* brackets micromegaly with progeria. Nevertheless, we can only see in this mixed likeness and unlikeness of progeria to acromegaly a corroboration of the view that we have here taken on the pathology of dwarfism, gigantism, infantilism, and senilism.

Summary and Conclusions to Part IV.†

In the early palæolithic days of human development there was as great or greater diversity in the forms of mankind than there is now.

The evidences upon which our conception of prehistoric man are based are in the main of four kinds, to wit: (1) More or less fossilised fragments of skeletons; (2) carvings of the human figure; (3) tradition (folklore, fairy tales, etc.); (4) that which is derived from the recapitulatory features of human development.

* Vol. vi, p. 473.

† The views which have been held, and are now held, of the nature and classification of prehistoric man are so diverse and so fluctuating that it is not possible to dogmatise on the subject. It must therefore be understood that the seeming confidence with which we write is solely for the sake of brevity and clearness. We approach this subject from the points of vantage of phylogeny and of pathology, and use the facts of palæontology as supporting evidence.

All these evidences point to the conclusion that out of the many modifications of the genus *Homo* two strongly marked and widely different types stand out conspicuously.

One of these may be termed the *simian type*. Men of this type were big and muscular, of a stooping figure, and were generally constructed on an uncouth, clumsy pattern. Of a coarse physiognomy, they possessed heavy, overhanging brow ridges, big, shapeless noses, strong projecting jaws, the alveolar portion being especially prominent in order to give room for the large and well-developed teeth. Though the forehead was receding the cranial capacity was not greatly inferior to that of modern skulls.

There is every reason to believe that this type is a degenerated type, a stock whose development had deteriorated in the direction taken by the anthropoid apes. They were, in all probability, wild men, unacquainted with religious beliefs or with methods of sepulture, whose remains, therefore, have been found covered under river deposits, or in caves among the bones of the cave bear and other inferior animals.

Men of this big, simian type, savage, brutish and unintelligent, have given rise to the legendary stories of the giants of the fairy tales.

The other type may be termed the *child type*, for it roughly corresponds to the child stage of human development. Palaeolithic men of this pattern were smaller in size, more delicately formed, with long bodies and short limbs. Of fair intelligence, they employed devices for the hunting of lower animals, and showed some skill in the arts, for we base our knowledge of them to a large extent upon the figures which they cut upon the tusks of the animals they killed. It is highly probable that they possessed the rudiments of religion, were able to communicate ideas by means of an archaic picture-writing, and disposed of their remains by burning, or by some form of burial. Tradition bears witness to their small size, to their intelligence, and points to the conclusion that this intelligence was of an infantile order, uncertain, capricious, expressing itself at times in child-like pranks of mingled fun, good nature, and mischief.

This child type represents the line along which our own development has proceeded, partly, no doubt, by slow progress from lower to higher, partly by occasional saltatory changes, and partly by admixture of the dwarf stock with other stocks.

It would be wrong to suppose that these two types, the simian and the childish, have completely died out, for, as a matter of fact, in some parts of the earth's surface the conditions of existence are of such a nature as seriously to retard the progress of human life.

In such circumstances a kind of man exists differing in no very important particulars from the Neanderthal man. Thus among the great arid, inhospitable wastes of Australia the indigenous tribes hunt and fish, adorn themselves, propagate, and murder much as did palæolithic man. Moreover, their bodily configuration corresponds in many important particulars with those of the simian type who lived in Europe in the early Stone Age. They represent a deteriorating stock, and their characters are largely degenerate characters.

So also among the forests, deserts, mountains, and islands of many parts of the world we still meet with little people whose mental, moral, and physical peculiarities roughly correspond with all that we know of the childish type of prehistoric man on the one hand, and with those of the modern child on the other hand. They are, to all intents, not degenerate men, but unfinished men, with, perhaps, a spice of degeneracy thrown in.

The human being, like the sweet pea or the pigeon, is liable at times to revert or throw back to a by-gone state. In other words, man, like all other forms of life, is dependent upon precedents for his advance in the scale of creation. And if at some stage of his development his environment be of such a nature as to imitate and exaggerate that which was normal at a corresponding stage of his evolution, his development is liable to mark time, as it were, halting for a season, so as to stagnate into a state of so-called (symptomatic) infantilism. Or again, as a rare event, quite apart from environment, a lapse takes place in the process of body-formation during an important period of development. Development seems to be carried on to a certain point and the means of continuance is then forgotten, leaving the individual in a state which roughly corresponds with that paralleled in his evolutionary existence. If this act of racial forgetfulness take place during his infancy he will more or less correspond in his main features with his forbears of an early palæolithic stage of development. Certain details, it is true, may be left out of the picture, but the general outlines will be correct. He is then in a state of idiopathic or essential infantilism of the variety which is termed ateleiosis.

Now let us turn from the infantile state and infantilism to the senile state and senilism.

If anything should occur in the life of a man to precipitate senile degeneration, the same adherence to precedence which caused the unfinished man to resemble his prehistoric prototype of childish pattern will now cause him to assume the characters of prehistoric man of the degenerate or simian type.

This, indeed, is what happens when he falls into a state of normal old age. Second childhood is not of the progressive or infantile but of the degenerate pattern, such as we meet with in the Australian or in the palæolithic man of Spy, Neanderthal, Java, Corrèze, or Gibraltar. He becomes bowed in figure, more hairy, coarser, his muscular co-ordination is deficient, and he walks as if unaccustomed to that acquirement; his eyebrows become heavy, his nose enlarges, and his whole aspect assumes an anthropoid type. This does not mean that man has ascended along these gorilla-like lines, but that for æons of time it has been the custom for degeneracy to take this form, and when, therefore, the degeneracy of old age sets in, the inherent conservatism of developmental methods insures that it shall tend to resume the original degenerate pattern.

So also, and still more emphatically, when a man falls into a state of senility at an abnormally early age, his more plastic tissues take the impression of the old prehistoric mould still more completely: and being a degenerate condition the throw-back or reversion is of the hideous simian type.

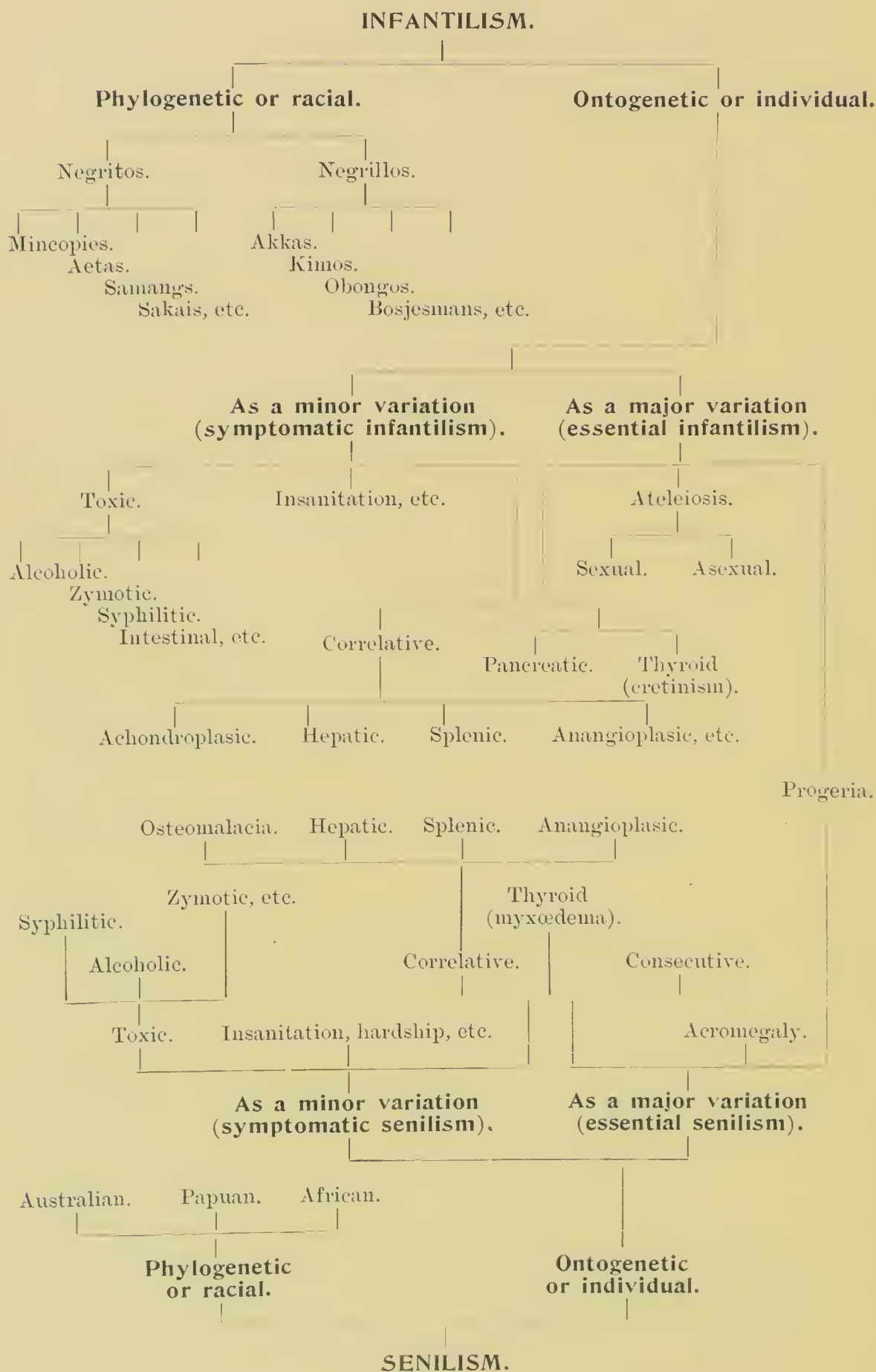
This reversion has received the name of "acromegaly." Acromegaly, as a form of premature senility, or senilism, is therefore in many respects a caricature of normal old age. In this disease some of the characters of the old savage stone-using man of early prehistoric days are revived. Acromegaly therefore forcibly reminds us of the apes, so that some of those who first described it were astonished at the resemblance, and many of its characters are similar to those of the aboriginal Australians, who are a people in a state of racial senilism.

Since the above was written, Prof. Keith, in an important paper entitled "An Inquiry into the Nature of the Skeletal Changes in Acromegaly,"* states that Dr. Barnard Davis was the first (in 1867) to recognise the resemblance between the crania of Neanderthal man and of acromegaly. Prof. Keith shows that in many other ways beside those which have been mentioned here there is a close correspondence between the changes which take place in acromegaly and in the growing anthropoid ape, and are noticeable in Neanderthal man.

But the conclusion he draws from his observations is not that there is an atavistic connection between them, but that the correspondence is probably in all cases due to the action of hormones arising from the exalted action of the pituitary body.

* 'Lancet,' 1911, vol. i, p. 993.

CLASSIFICATION OF GENERAL INFANTILISM AND GENERAL SENILISM.



PART V

GENERAL SUMMARY AND CONCLUSIONS

General Summary and Conclusions

SICKNESS in the past, as among savages of the present day, was a supernatural visitation. It was the work of demons, who were to be exorcised by incantations, and their position in the body rendered untenable by means of filthy and gruesome concoctions. These devil-terrifying remedies were administered by mystery men, who donned a special garb and took great care that none but a privileged few should be initiated into the secrets of their craft. Though in course of time medicine has been gradually emancipated from make-believe and quackery, traces of this old conception still cling about the medicine of the present day. There still lingers, chiefly in country districts, a feeling that in the treatment of disease medicine in some form is essential to success, and to be effective must be nauseous; that medical art must be conducted with ceremony; that signs must be used which have for their purpose the preservation of a glamour of mystery; and that the medicine man must adorn himself with a distinctive clothing. But in no respect does the old time odour of sanctity and magic continue more pertinaciously than in our conception of the nature of many diseases. Though it is true that we no longer regard them as supernatural, we have not yet got so far as to assign them a place among natural phenomena. We think of disease as something not exactly tartaric, but as suspended above or below the realm of the natural, and as being akin to the preternatural or the unnatural. In short, medicine is an isolated science, separate from theology on the one hand, and from biology on the other; it is the abode of mystery where the cobwebs of obsolete theories still linger in spite of the rapid alterations which have been effected by recent science.

We have seen how the extrinsically produced infirmities of the body have been brought under the sway of the biologist. It cannot too emphatically be insisted upon that intrinsic diseases must be equally biological. They cannot be either supernatural or unnatural, but must of necessity be no more than the expression of the common

laws of life, and have their springs either in contemporary events or in events which have influenced us in the past.

If we put on one side bacteria-produced diseases, and group together all those maladies which are independent or only partly dependent upon external sources, we find that by far the majority are merely the extremes of normal biological processes. Most of them seem to be affairs of development or of growth. Growth is defective or excessive; development is too tardy or terminates too soon. Such extremes have received the names of "variations." These variations are of two kinds. Some are of very pronounced degree and of rare occurrence, seem to arise spontaneously, and show hereditary tendencies. Others, of minor degree, are more common, are partly the result of a cause or of causes, and are never hereditary.

These variations are so ubiquitous that no detail of organic life but is liable to their occurrence. Every plant, every animal, every organ, every function is liable to variation. Moreover, this variation may occur in one of two ways. It may be an example of progress carried to excess and be a progressive variation, or it may be a reversion and constitute a regressive variation. Hence it will be understood that growth and development cannot escape liability to these biological extremes; they, too, are subject to variation, and it is these variations which constitute disease.

Let us now take a fresh start. We see that all the higher members of the animal kingdom have a tribasic constitution. A man, for example, consists of three structural units. He is composed in the first place of cell units; but cells congregate together to form organs, and organs are the units which, collected together, form the whole man, which again is the unit of another body, the body politic. Each of these units, though dependent one upon the other, is in many respects independent. This independence is manifested in their growth and in their development, for each cell has its own rate of growth and its own duration of life; each organ has its own standard of size and of endurance; and each individual man varies in stature and in longevity from other men. But it must be evident that if the growth or development of the cell differ so widely from the growth or development of the organ, and these again differ from the growth or development of the whole man, so also will their disorders differ. This is fully recognised when either of the structural units is affected with bacterial disease, but it is also equally true of those diseases which are variations. Thus if a few cells grow to excess, forming the progressive variation we term an innocent growth, we have a very different disease from the similar

variation of an organ, such as that of the thyroid gland in Graves's disease, or of the spleen, or liver when it undergoes simple numerical hyperplasia; and this overgrowth of organs differs again in its results from that overgrowth of the whole individual which constitutes simple gigantism.

Still greater difference is to be observed when the variation is one of development. Thus when a few cells sink into old age while the cells round them are still young the product of their prematurity is a cancer, but when an organ falls into a similar state of dotage the result, though equally disastrous so far as function is concerned, presents many points of difference. It gives rise to a condition which, if it occur in the liver, we term "cirrhosis," in the kidney "Bright's disease," in the thyroid gland "fibrous goitre," and so on; but a similar old age distributed more or less evenly over the whole body presents itself very differently from the senility of the cell and of the organ. Indeed, it requires some effort to recognise that acromegaly is the same process affecting the whole individual as that which gives rise to cirrhosis when it occurs in the liver, and cancer when it occurs among cells.

To understand what is the common factor in these different aspects of premature senility we must ask ourselves what constitutes normal old age.

Old age is the terminal stage of development and the beginning of dissolution. It is characterised by a process of steady deterioration of function and structure. The accomplishments of childhood, of youth and of maturity gradually disappear. There is a reversal of development, so that the more complex cells, which began life as round masses of nucleated protoplasm, gradually lose their angles and processes and once more tend to return to their primitive simplicity. This progressive denudation, occurring simultaneously in function and in structure, continues among the various cells of the body until at last highly important cells presiding over the elementary functions of circulation or respiration become so simplified that their special career can no longer continue, and life is brought to a close. The lower class elements escape this process of peripheral absorption for they are already in a state of extreme simplicity; being already of low degree they need fear no fall, so that while the high-class cells around them are losing their substance and their occupation they continue their work unimpaired. Now one of the functions of these more humble cells (lymphocytes, endothelial cells, fibroblasts) under normal conditions is that of phagocytosis. It is their office to clear away the *débris* of the body and to deal with the

non-virulent foreign particles and invasions. Hence, when old age creeps upon the tissues, and the gland-cells are everywhere undergoing peripheral decay, these phagocytic cells increase largely in numbers. In organs in a state of advanced senility they may be seen liberally sprinkled among the cells peculiar to the organ. Hence normal senescence is a reversal of development which is manifested by recession of the higher types of function and by a corresponding peripheral decay of the cells responsible for that function.

Now let us suppose that the same process of simplification is going on, not in the body as a whole, but in one isolated part of the body, while the rest is still in a state of efficiency. Evidently the higher kinds of cells will be able to attain a far more advanced stage of retrogression. They will not only be on their way to the stage of the round embryonic type, but will nearly reach that stage. This is what happens when cells become cancers. They reverse their development (become prematurely senile), and, like all embryonic cells, multiply prodigiously, pushing their way along the paths of least resistance and so wander *viâ* the open channels of the lymphatics into other parts of the body. Let the same process of embryonic decadence take place in an organ, such as the liver, and again we see simplification of special cells carried to a far higher degree than is possible in the widespread process of normal old age. The phagocytes, which in cancer are destined to form bands of interlacing fibrous tissue, in cirrhosis of the liver become the fibrous meshwork which we see encircling the lobules. But the simplification of specialised cells can never be carried to such lengths in the liver as in cancer, and for this there are two reasons. One of these is that when the angles of a certain number of liver-cells have been rounded off, and their function correspondingly reduced, the work which is demanded of the liver by the rest of the body must come to an end, so that the individual dies long before the last stage of senility has been reached. The other, and chief, reason is that the biological prototype of the single cell is a protozoon animal, whereas the phylogenetic equivalent of an organ is a metazoon animal, and so great is the influence of precedence in the economy of the body that we may be sure that when a cell degenerates it will go back to the protozoon stage, but when an organ loses its restraints of development it is not likely to carry its reversal beyond the metazoon stage. It still remains an organ, though it may be an organ of most primitive description. But now and then, as a rare event, the individual cells of the liver, having arrived at the limits

of metazoon independence, go over the border and proliferate as cancers.

So much for premature old age of cells and of organs. In both cases there is a reversal of development, the cell losing its special qualities and returning to primitive savagery as a cancer-cell, and the organ returning to the condition characteristic of the first organs. So also with the whole man: he, too, in premature old age reverses his development, harking back to an earlier period of development and actually resuming the form of primitive and degenerate man. Degenerate man of the earliest Stone Age was big and tall, unable to stand erect, the possessor of large supra-orbital ridges, a big, shapeless nose, heavy jaws, and ill-formed, coarse, unprepossessing features. His hands and feet were big and clumsy, and his whole structure was cast in a rougher mould than that of civilised man of the present day.

This picture of palæolithic man of simian type is in every respect applicable to acromegaly, which we therefore regard as a regressive variation of development—a premature senile decay of the human animal.

We have now rapidly gone through the principles which underlie the subject of premature old age. We have seen that the cancer, the cirrhotic liver, and the man with acromegaly, though seeming to have nothing in common, are in reality all examples of the same morbid variation of a biological process. Though there is as much difference between these forms of premature old age as of the old age which attacks the amœba, the sponge, and the man, they are all fundamentally alike.

We have so far touched upon the subject of premature old age or senilism, but have said nothing, or next to nothing, of delayed development or of infantilism, nor have we more than alluded to the very wide subject of the two extremes of growth. Of these we can do no more than give examples, first premising that they also must be dealt with on strictly biological lines. And our conception of these different forms of variation is prejudiced at the outset by our preconceptions. Thus if we take as our example the disorders of growth and development of the blood we are at once hampered by the fact that the blood is not commonly regarded as an organ; but having overcome this little difficulty and settled that it is indeed an organ, we know of a surety that, like every other organ, it must be liable to vary in the number, in the structure, and in the quality of its constituents. This we must regard as an axiom not to be gainsaid. But having decided that each of its constituent parts is

liable to extremes of growth and of development, we next ask ourselves in what way do these extremes manifest themselves—What are their symptoms?

Let us first take the red constituents and suppose that we have to do with an overgrowth—that the erythrocytes have undergone numerical increase to a pathological extent. A little consideration will tell us that this condition must result in plethora. The fulness of blood will be seen in a red, purple, or bloated face, and in a tendency to apoplexy, in a full habit of body, and in an increase in the number of the red discs, as shown by the hæmocytometer. Under this description we have no difficulty in recognising the modern disease polycythaemia. But when we glance in a similar conjectural fashion at the morbid state which is produced by overgrowth of all the constituents of the blood, it requires a distinct effort to realise that we are dealing with that very common disorder known as chlorosis. Yet it is now recognised that the puffiness, the œdema, the headaches, the embarrassment of the heart, the hæmorrhages, which are so conspicuous in that malady, can all be accounted for by over-distension of the heart and blood-vessels with an excessive and somewhat impoverished supply of blood.

So far we have not experienced very much difficulty in reconciling our ideas with those which are commonly associated with well-known disorders. But when we apply our principles to the degenerative affections of the blood our way is at once obstructed with very grave impediments. These are for the most part the outcome of prejudice. We have become so accustomed to looking upon leukæmia and upon pernicious anæmia as disease processes standing alone, having no relation to any other disorder except, perhaps, of a causative nature or as accidental accompaniments, that our preconceptions receive a shock as it dawns upon us that their structural characters and their symptoms are those of a disease of development, and that they are indeed without a shadow of doubt premature senile degeneration of blood. Nothing can at first sight seem more ridiculous than to state that a disorder which brings about excessive waste of the red constituents of the blood should be fundamentally the same as that which causes the increase of tissue in hypertrophic cirrhosis of the liver, or that the process which gives rise to such extreme scantiness of red discs in the one disease is based on the same principle as that which leads to the equally extreme over-abundance of leucocytes in the other disease. But these difficulties vanish if we keep constantly in view our conception of senility as a simplification of higher cells and an increase in phagocytic and multiplying properties of lower

cells. A process of this nature going on in one organ will produce a certain result, and going on in another organ may produce results which seem to be diametrically opposite, the difference depending not only on the nature of the change, but upon the nature of the organ affected. Thus in the liver of hypertrophic cirrhosis the lower-class elements consist largely of fibroblasts deprived from the connective tissue in response to the great demand for phagocytes brought about by the presence of a large number of degenerating liver-cells. These having done their work of phagocytosis return to their resting stage and become once more the constituents of fibrous tissue. But meantime, so greatly have they increased in number, that whereas in the normal liver they formed no more than a thin and delicate supporting tracery for the liver-cells and their vessels, they are now swollen out into thick bands constituting the most conspicuous feature in the diseased organ.

In pernicious anæmia we have a widely different tissue to deal with, and the results are correspondingly different, though they are brought about in the same way. The blight of senility falls upon the red constituents alone, causing them to retrace their development till they arrive at their embryonic stage. But a nucleated red cell floating in the blood-stream is as abnormal a constituent of mature human blood as is a nucleated blood-cell of an amphibian. It is, therefore, speedily dealt with by the phagocyte cells of the marrow and spleen. This vicious half circle of imperfect formation and accelerated destruction having continued its deadly swing for a few months, the blood is at last left with nothing but fragments of red corpuscles to carry on its duties. Meanwhile the phagocyte cells of the lymphocyte order, not being implicated in the morbid senility, flourish upon the misfortunes of their red neighbours, with the result that the spleen undergoes a manifest increase in size.

In leukæmia the state of affairs in regard to the two kinds of elements, the red and white, is reversed. It is now the turn of the white cells to deteriorate. They therefore multiply, and as they multiply their phagocytic property becomes impaired, so that in a short time the blood-vessels are filled with white corpuscles, most of which are embryonic, and in a state of degeneration, or are both embryonic and degenerate.

It is evident that we should be gravely misled if we attach any vital importance to mere accumulation of cells in the blood in distinguishing between the pathology of pernicious anæmia and leukæmia. These differences are not basic, but are the outcome of mere accidents of locality. Obviously the hyperplasia of the

spleen in the one disease corresponds with the hyperplasia of the marrow in the other, for both indicate a vast collection of embryonic cells at the source of supply. The nature and method of the disease process is the same in both cases.

So also, after the same fashion, with other diseases of the endogenous group. We are not concerned with a number of detached disorders, each isolated from its fellows by an unbridgeable chasm, but each owes its individuality to some secondary characters, and has its primary or fundamental characters in common with many other disorders. It stands out only as a summit or peak, its base being incorporated with the bases of other diseases to form a great range or system.

In distinguishing between the derangements of growth and derangements of development we have always to keep it in mind that growth is quantitative and development qualitative. Consequently there is as much difference between these disorders as there is between those protrusions of the earth's surface which form mountains and those which constitute volcanoes. It is not possible for growth to be greatly excessive without that excess entailing some distortion of development, nor can development proceed too far without some loss of the restraints of growth and consequent redundancy of tissue. Evidently, therefore, these two morbid processes, exuberant growth and premature degeneration, cannot be rigorously separated, but admit of all manner of gradation between them. It seems pretty certain that simple overgrowths which occur exclusively during progressive development must be regarded as progressive variations, whereas overgrowths which have their origin in degenerative processes are regressive variations. Perhaps the best example of these two kinds of overgrowth is furnished by the thyroid gland, which may enlarge at puberty to form the parenchymatous goitre of Graves's disease, or it may undergo simple enlargement in middle age, constituting the parenchymatous goitre of regressive development. The one is due to an impulse of growth having its springs in the rising tide, and the other is due to a loss of growth restraints incidental to the falling tide of development.

We have now given some illustrations which may serve as examples of the diverse ways in which the manifestations of any disease of growth or of development are shaped by normal peculiarities of structure and function. Indeed, so intimate is the relation between the normal and the abnormal that it is only the incongruity of the growth or of the development which constitutes

the disorder. It is normal for the liver-cells progressively to deteriorate in old age, and for the scavenging cells to clear away the products of decay ; but it is abnormal for this process to go on during middle age, when the body, as a whole, is at its prime. It is a physiological process rendered pathological by dislocation from its proper setting. Evidently, therefore, in order to understand the constitution of a disorder of growth or of development we must look closely to its physiological antecedents. Thus growth will be most likely to become excessive at about the period of its greatest relative physiological activity, and degeneration will be most likely to set in prematurely during the period of normal decline. Hence we must look for overgrowth of the pylorus shortly after birth, when the stomach, a new and untried organ, first comes into use, springing at a bound from a state of inaction to one of great relative activity. Overgrowth of the skeleton will be most likely to appear during early infancy, when normal osteogenesis is most active, and is dependent upon supplies of material which are liable to fall short of, or to exceed, their proper quality and quantity. Evidences of this skeletal overgrowth would be far more manifest near the ends of the bones than elsewhere, because it is at the epiphyses that normal growth is most vigorous, though periosteal hyper-activity would also be present as well. The reason why this osteogenetic excitement fails to culminate in increased osteogenesis admits of very simple explanation, which has been dealt with under the heading of "skeletal overgrowth" or rickets (p. 422). Premature senile degeneration of the skeleton, shown by retracement of its development, will, of course, appear, as a rule, during or after middle age. This has been discussed in the chapter entitled "Senilism of the Skeleton," or Osteomalacia and Osteitis Deformans (p. 440).

But we cannot take a really satisfactory grasp of these and the similar disorders of other organs without realising to the full the meaning of the two kinds of variation—major and minor. We shall then understand the relations of achondroplasia to rickets, of hypertrophic cirrhosis of the liver to atrophic cirrhosis, of tabes dorsalis to Friedreich's ataxia, of the large white kidney to the small, red, granular kidney. We shall realise without any unpleasing shock that the status lymphaticus, rickets, the goitre of Graves's disease, chlorosis, childish obesity are the results of the operation of a similar process of progressive variation affecting different organs on a similar principle.

But our subject is not quite so simple as appears on the surface, for serious complications arise from the circumstance that premature

senescence, or senilism, does not always arise primarily as a mere precocious termination of an otherwise normal cycle of development. It may be secondary to some prior morbidity. There are, indeed, two conditions which markedly facilitate its onset. One of these is simple overgrowth. We have already noticed that the condition of overgrowth necessarily implies some weakening of the restraints of development, and this is especially true of the overgrowths of the declining stages of development, which are, indeed, invariably degenerate. Evidently, therefore, the fact of overgrowth constitutes a strong predisposition to degeneration, and accounts for many of the cases of degenerative hyperplasia which occur in early life. In all probability most, if not all, of the cases of degenerative hyperplasia of the pylorus, of pseudo-hypertrophic palsy of the muscles, of hypertrophic cirrhosis of the liver have their start in a prior overgrowth. The course of events is then similar to when a cancer (degeneration of cell) has its source in an adenoma or other simple overgrowth of cell groups.

But of far more importance in facilitating the onset of presenility is morbid defect of development, or infantilism. An organ so affected does not run a longer course of life because of its prolonged infancy, but, on the contrary, terminates its existence much sooner. The middle period of development seems to be cut out so that development proceeds at a leap from the infantile stage to the senile, from infantilism to senilism. It is in this way that we account for most of those cases in which degeneration sets in during early progressive development. Hence, the cancer of juvenile or middle age in all likelihood invariably springs from some collection of aberrant cells still in a state of imperfect development. And the Bright's disease, liver cirrhosis, insanity, paralysis, which comes on precociously in young subjects is of this same nature. This secondary form of senilism may sometimes be recognised by the detection of the prior infantilism, or by the fact that the degenerate organ is small in size, so that special names (*e. g.* dementia præcox, Rose Bradford kidney) have been given to the senilisms which arise in this way, to distinguish them from the primary form.

We have sketched our subjects in the broadest of outlines, leaving out many highly important details so as not to weaken the general impression. We may continue on the same plan in respect to treatment. Experience teaches us that certain agents or circumstances have a retarding or accelerating effect upon growth or development; and we find that these same agents, or their allies, play an important part in the aggravation or the removal of the maladies of these

processes. For example, that class of conditions which we associate with the word "hygiene" tend to prolong life and to delay the progress of normal old age, and are recognised as of service in mitigating the disorders of development. Arsenic, which acts as a tonic to young children, improving their nutrition and facilitating increase of tissue, seems on *à priori* grounds to be unsuitable for growth which is already excessive. It is, therefore, but to be expected that arsenic should be of no use or should be positively harmful in the overgrowths such as chlorosis, polycythæmia, and Graves's disease.

On the other hand, the same drug is useful in the degenerations. Indeed, it is probably the only substance which has been found to act as a remedy in Hodgkin's disease, in pernicious anæmia, leukæmia, osteomalacia, arthritis deformans, or cancer. It is true that the treatment of these diseases affords much scope for the play of the imagination, yet it appears to be of some significance that while reliable observers have found that arsenic is harmful when given for certain excesses of growth, they are equally, or still more emphatic, in vouching for its good effects in the degenerations, whereas we can find no example of the reverse experience. If this action of arsenic were solely imaginary we should expect that the testimony would not be so consistent.

Of similar significance is the effect of pregnancy. This, generally speaking, ameliorates the overgrowths of organs, and aggravates their degenerations.

As development advances into old age the tissues apparently become more susceptible to microbial attacks. So also presenile degeneration and defective immunity go together. Hence the kidney crippled with the degeneration of chronic Bright's disease is more open to the attacks of the organisms which produce nephritis, the leukæmic spleen readily inflames, and the fibrotic lung often becomes tubercular.

Advantage is taken of this vulnerability of degenerated tissues as a means of cure. Thus X rays, which check the growth of normal cells and ultimately disintegrate their cytoplasm, will have this effect much sooner when the cells are already degenerate. Hence they sometimes destroy the cells of cancer or reduce the swollen glands of Hodgkin's disease, or the leucocytic hyperplasia of leukæmia, without giving rise to perceptible damage of the healthy tissues around them.

The use of erysipelas toxins and other toxins in the treatment of cancer is founded upon similar reasons, for while these toxins are inimical to the healthy cells of the body, they may be positively

destructive to cancer-cells and the embryonic cells of leukæmia or of Hodgkin's disease.

So far we have been mainly concerned with the cell in its individual capacity and with the organ; the same principles apply to the same diseases of the whole man.

There is reason to believe that our direct line of ascent from the brutes came through a type of the genus *homo*, which in many respects corresponded with that of the infant, who is contemporary undeveloped man. Like the modern baby, he was of small stature, possessed a relatively long body, big head, and short limbs, the proximal segments being short in comparison with the distal. The hands and feet were small, the face broad and flat, the nose small and *retroussé*. We have noticed how invariably development proceeds from precedent to precedent. Whenever, therefore, anything takes place to delay or arrest the development of the body, it gives rise to a state which corresponds in some important respects with that characteristic of the man of short stature who lived in the days of the rougher flint implements. Rickets and achondroplasia, which are the outcome of interference with the growth of the skeleton in the first place, and of adaptation or correlation of the growth of the soft parts in the second place, result in a short-limbed, big-headed dwarfism. This dwarfism, moreover, has not only the characters of the prehistoric type in regard to length of limbs, but also in the relative length of the proximal to the distal segments. So also when the sex organs ripen too soon and the whole body undergoes a spurt of correlative growth in keeping with it, the result is that the human being is often not like other men, but remains permanently of the prehistoric, short type. But of no condition is this generalisation more true than that of general infantilism, and particularly of that form which is essential and has received the name of "ateleiosis." This consists in a conspicuous delay of development of such a character that in well-marked cases the stature and proportions remain permanently childish. Like all biological extremes (variations) ateleiosis tends to be associated with sex deficiency. Sometimes there is absolute neutrality (asexual ateleiosis), but as a rule the development of sex is merely delayed, puberty arriving some years after it is normally due. It is the sexual variety which the more closely corresponds with our ideas of the short type of palæolithic man. Indeed, we can imagine a very close resemblance between the little ateleiotic man with his short limbs, his small hands and feet, his big head, and his mature sex condition on the one hand, and men of some of the tribes which

inhabited Europe and made the clever drawings of animals and man in the Stone Age.

The little prehistoric people just referred to in all probability lived side by side with men of much coarser type and greater stature. Some of these big-boned people had receding foreheads, overhanging eyebrows, widely spread shapeless noses, and heavy jaws. Sparsely covered with hair and unable to maintain an upright attitude they represented races which had either not yet arrived at the evolutionary status attained by the short people, or were the degenerate offshoot from a more civilised stock. But one thing seems clear, and that is that the distinguishing characters just referred to are brute characters, such as can be recognised in the jaws, teeth, eyebrows, attitude of the dog, the cat, the monkey, and other inferior animals.

Now we have seen that when cells or organs degenerate they rarely go back beyond the limits of their phylogeny. In other words, the cell does not (or cannot) retrace its ancestry beyond the amoeba stage, nor does the organ beyond the metazoan stage. So also when the whole man retrogrades in his development his retrogression is limited. He exhibits the characters which were at one time the characters of his remote ancestor, palaeolithic man of simian type, which again were derived by him from his ancestors, the brutes. Traces of this reversion can be detected in some old men, whose prominent eyebrows, large shapeless noses, diffuse hairiness, and inability to stand erect have their precedents in our simian forbears. But all these reversionary or degenerate characters occur to a far more conspicuous degree in the disease acromegaly. There is, indeed, good reason to believe that acromegaly is a reversion, a regressive variation of major degree in which the body is concerned as a whole. It is, therefore, a presenile degeneration or senilism having the same relation to the complete man that cirrhosis has to the liver as an organ, and that cancer has to the individual cell.

We must now once more return to the cancers. It has been said that the cancer-cell is a cell which has reversed its development. This statement requires some modification. Some cancers (cylindromata) are far from having arrived at unicellular independence. The special characters ingrained by long ages of custom cannot be annulled within the course of a few weeks. Nevertheless the generalisation holds good. They are on the way to the goal of independence, and the nearer they get to it the more malignant are they. Indeed in the round-celled sarcomata and the spheroidal-celled carcinomata organisation is at a minimum; the emancipation

of the cell is almost accomplished, and these, therefore, are the most virulent of all cancers.

So also with organs. An organ is never degraded to such a level that its special characters become unrecôgnisable. Among the round-cells and the cell *débris* which constitute the ruins of a liver or kidney we can always trace the outlines and many of the details of the perfect structure, and we know that these will be present even if it were possible for life to continue until every cell had been brought under the plough of degeneration.

Similarly with the whole man. Though theoretically his degeneration will carry him back along the line of his ancestry to the period of the earlier complex animals, yet in reality he gets no further than the anthropoid stage. Moreover reversion is irregular and partial, for death invariably steps in to terminate the downward career long before it reaches its limits.

In every case, no matter whether the unit involved be a cell, an organ, or a man, senilism consists in a compromise between the degenerating or reversing tendencies on the one part and the conservatism born of long centuries of habit on the other part.

We have now reached the end of our book. It is still very far from complete, for we have said nothing or next to nothing of the disorders of the supra-renal capsules, the lungs, the prostate, the pancreas. Still worse, we have left out the important subject of the temporary disorders of growth and development such as arise during infancy and childhood and are recapitulatory in nature. Thus incontinence of the urine or fæces, which is a contemporary malady of childhood, is almost certainly but a passing reminiscence of a state which was normal at an early stage of human evolution. Similarly with some of the mental and moral delinquencies of childhood, these, too, serve to remind us that there was a time in our evolution when lying, stealing, and cruelty were consistent with a normal state of human society.

But we have written enough. To the best of our ability we have attempted to make a rough sketch of the principles which underlie and account for the diseases of growth and development, and we have signally failed in our task if we have not succeeded in showing that that which constitutes disease at one time or from one aspect is normal at another time or from another aspect—that the same process may be either biological or pathological, according to the point of view from which we regard it.

INDEX

- ACEPHALY, 231, 323
 ACHONDROPLASIA, 424
 — anatomy of, 425
 — associated with cretinism, 429
 — — with Graves's disease, 429
 — — with obesity, 429
 — — with rickets, 429
 — heredity in, 429
 — — transforming, in, 429
 — in lower animals, 429
 — overgrowth in, 425
 — results of, 428
 — rickets, relation to, 424, 429
 — symptoms of, 428
 — as a variation, 428
 — varieties of, 425
 ACROMEGALY, 666
 — acute, 680
 — alcohol as cause, 666
 — arsenic in, 667
 — associated with aortic stenosis, 667
 — — with diabetes, 667
 — — with epilepsy, 667
 — — with feminism, 539, 673
 — — with genital aplasia, 667
 — — with Graves's disease, 667
 — — with myxedema, 667
 — — with pernicious anæmia, 667
 — — with syringomyelia, 667
 — causes of, 666
 — chronic, 680
 — correlation of growth in, 478
 — course of, 667
 — diagnosis from giant extremities, 225
 — feminism in, 539, 673
 — galactorrhœa in, 670
 — gigantism, relation to, 678
 — Graves's disease in, 668
 — hair in, 673
 — heredity in, 667
 — — transforming, in, 667
 — infantilism in, 673
 — infectious fevers as cause of, 666
 — lead as cause of, 666
 — masculinism in, 673
 — osteitis deformans in, 671
 — osteomalacia in, 671
 — pathology of, 668
 — perspiration, profuse, in, 670
 ACROMEGALY, pituitary body in, 668
 — progeria opposed to, 656
 — remissions in, 667
 — senilism in, 673
 — simian characters in, 673
 — skeletal overgrowth in, 671
 — splenomegaly in, 671
 — sterility in, 667
 — symptoms of, 670
 — syphilis as cause of, 666
 — trauma as cause of, 666
 — treatment of, 667
 — as a variation, 666
 ADAPTATION, 109, 474
 — in senilism, 62, 632
 — relation to variation, 110
 — — to correlation, 477
 ADENOMATA, 149
 — in liver cirrhosis, 290
 — of thyroid gland, 467
 ADIPOSIS dolorosa, 504
 ADOLESCENCE, 31
 — chlorosis in, 374
 — consecutive nervous degenerations of, 326
 — insanity of, 327
 — parenchymatous goitre in, 357
 ADOLESCENT insanity, 326
 AGE in arterial disease, 351
 — in blood degenerations, 393
 — in cirrhosis, 269
 — influence upon growth, 10, see also *Old age*.
 ALBINISM as a major variation, 103, 105
 — as a minor variation, 103, 107
 ALBUMINURIA, hereditary, 308
 — in pregnancy, 305
 ALCOHOL, action of, 63
 — — as a drug, 64, 66
 — — as an environment, 104, 111
 — — as a food, 64
 — — as a narcotic, 62
 — — as a toxin, 49, 60, 62, 69
 — as cause of abortion, 77
 — — of acromegaly, 66
 — — of acute yellow atrophy, 268, 277
 — — of arterial disease, 347, 350
 — — of Bright's disease, 304
 — — of cancer, 162

- ALCOHOL as cause of cirrhosis, 268, 290
 — — of degeneration, 62, 209
 — — of gastric degeneration, 339
 — — of general paralysis, 330
 — — of infantilism (general), 483, 563, 583
 — — of insanity, 66, 316
 — — of muscular dystrophy, 248
 — — of obesity, 512
 — — of senilism (general), 633
 — — of sterility, 77
 — — of tabes, 329
 — — of telangiectases, 148
 — changes produced by, 63
 — effect of, combined with lead, 67
 — — on the fœtus, 76
 — — on savage races, 548
 — immunity to, 50
 — in infantilism (general), 337
 — in liver cirrhosis, 104, 290
 — mortality due to, 64
 — relation of, to degeneration, 67
 ALCOHOLISM, periodic, 68, 122
 — — hereditary tendency to, 124
 AMAUROTIC family idiocy, 326
 AMAZONS, 541
 AMENORRHŒA in degenerative hyperplasia
 of the uterus, 360
 — in overgrowth of uterus, 355
 ANÆMIA, aplastic, 379, 413
 — — course of, 380
 — — features of, 379
 — — sex in, 380
 — in rickets, 424
 — lymphatic, see *Hodgkin's disease*, 389
 — pernicious, 386, 412
 — — age in, 394
 — — arsenic in, 389, 412
 — — associated with acromegaly, 667
 — — — with Bright's disease, 398
 — — — with cancer, 403
 — — — with liver cirrhosis, 397
 — — — with osteomalacia, 449
 — — — with sexual precocity, 402
 — — — with spinal cord fibrosis, 399
 — — — with stomach disorders, 399
 — — biology of, 414
 — — causes of, 392
 — — classification of, 391
 — — clinical characters of, 412
 — — course of, 394
 — — depression as cause of, 393
 — — endemic, 392
 — — heredity in, 395
 — — in lower animals, 396
 — — lead as cause of, 393
 — — pathology of, 413
 — — phagocytes in, 387
 — — polycythæmia in, 387
 — — relations with cancer, 403
 — — resemblance to leukæmia, 388
 — — senile, 411
 — — spinal sclerosis in, 400
 — — structural characters of, 412
 ANÆMIA, pernicious, as a variation, 414
 — — varieties of, 391, 413
 — — splenic, 389, 391, 395
 — — heredity in, 396
 — — relation to cancer, 404
 ANANGIOPLASIC infantilism, 370
 ANDAMANESE, 552
 ANIMAL (complex), a collection of cells and
 organs, 27
 ANXIETY, ageing effect of, 35
 APES, anthropoid, characters of, 673, 679
 — — compared with man, 673
 — — development of, 676
 APLASTIC anæmia, see *Anæmia, aplastic*, 413
 ARSENIC, as cause of cancer, 162
 — — of liver cirrhosis, 269
 — effect of, on degeneration, 699
 — — on growth, 699
 — — on overgrowth, 699
 — in acromegaly, 667
 — in arthritis deformans, 465
 — in cancer, 136, 178
 — in chlorosis, 374
 — in leukæmia, 389, 415
 — in mycosis fungoides, 204
 — in osteitis deformans, 461
 — in pernicious anæmia, 389, 412
 — in polycythæmia, 369
 ARTERIAL sclerosis, 349
 — — age in, 351
 — — anatomy of, 352
 — — associated with Bright's disease, 307
 — — — with dementia paralytica, 333
 — — — with hyperplasia of the gums,
 298
 — — — with kidney disease, 298, 303
 — — — with liver cirrhosis, 279
 — — — with obesity, 515
 — — — with pernicious anæmia, 400
 — — — with tabes dorsalis, 333
 — — associations of, 349
 — — caused by age, 349
 — — — by alcohol, 347, 349, 350
 — — — by gout, 347, 350
 — — — by muscular exertion, 350
 — — — by syphilis, 350
 — — — by tobacco, 350
 — — causes of, 359
 — — classification of, 346
 — — exercise in, 353
 — — forms of, 349
 — — heredity in, 352
 — — in infancy, 352
 — — juvenile form of, 352
 — — pathology of, 352
 — — in progeria, 652
 — — varieties of, 349
 — — vicious circle in, 347
 ARTERIES, defective development of, 348
 — — — in general infantilism, 568
 — — degeneration of, 347, 349
 — — hypermyotrophy of, 347
 — — hyperplasia, degenerative, of, 348

- ARTERIES, hypoplasia of, 348
 — — causing chlorosis, 348
 — — degenerative, of, 349
 — — preceding sclerosis, 348
 — infantilism of, 348
 — in progeria, 652
 — senilism of, 348
 — undergrowth of, 348
 ARTERITIS deformans, 349
 — obliterative, 349
 ARTHRITIS deformans, 419, 440, 462
 — — age in, 463
 — — arsenic in, 465
 — — arthritis in, 465
 — — cell changes in, 464
 — — course of, 463
 — — heredity in, 463
 — — inflammation in, 465
 — — lactation in, 464
 — — menstruation in, 464
 — — pathology of, 464
 — — pregnancy in, 464
 — — prognosis of, 463
 — — structural characters of, 464
 — — treatment of, 465
 — — as a variation, 465
 — — varieties of, 463
 ASSOCIATION of characters, 93
 ASYMMETRY of brain, 322
 — of face, 90
 — of giant growths, 224
 ATAVISM in acromegaly, 673, 684
 — in ateleiosis, 622
 — in cretinism, 626
 — in microcephaly, 324
 — in sex precocity, 526
 ATELEIOSIS, 484, 585
 — asexual, 590, 597
 — — author's cases of, 602
 — — cases of, 597
 — — characters of, 608
 — — dentition in, 603, 608
 — — growth in, 603
 — — of childhood and puberty, 609
 — — of foetal origin, 599
 — — of infantile origin, 599
 — — ossification in, 608
 — — skeleton of, 606, 607
 — cardio-vascular system in, 589
 — cause, absence of, in, 585
 — developmental irregularities in, 589
 — diagnosis from common infantilism, 585
 — — from microcephaly, 589
 — features of, 585, 588
 — a freak of nature, 585
 — group of cases of, 586
 — heredity in, 589, 596
 — intelligence in, 606
 — nervous system in, 589
 — pathology of, 612
 — physiognomy of, 586
 — pituitary body in, 599, 602, 613, 656
 — proportions in, 589, 608
 ATELEIOSIS, radiogram of, 604
 — sex system in, 589-608
 — sexual, 590, 591, 598
 — — associated with asexual form, 596
 — — heredity of, 593-596
 — — as a reversion, 616
 — — senilism in, 662
 — — sex organs in, 608
 — — a sport, 585
 — — thyroid gland in, 589
 — — two varieties of, 590
 — — a variable disorder, 590
 — varieties of, 590
 ATROPHIC cirrhosis, see *Liver cirrhosis, atrophic*, 282
 ATROPHY, acute yellow, see *Liver, acute yellow atrophy of*, 272
 AUTO-INTOXICATION, 5
 BABYHOOD, 31
 BACTERIA, uses of, 5
 BANTI'S disease, see *Anæmia, splenic*, 391, 395
 BATES, giants, 42, 490, 491
 BÉBÉ, a case of general senilism, 637
 — portrait of, 638
 — post-mortem examination of, 639
 — skeleton of, 639
 — wax model of, 638
 BILE-DUCTS, blocking of, associated with cirrhosis, 280
 — new, in cirrhosis, 286
 BILIARY calculi as a cause of cirrhosis, 281
 — cirrhosis, see *Liver, cirrhosis of*, 284
 BIOLOGY of disease, 7
 BIRTH-RATE, effect of depression and emotion on, 77
 — — of syphilis on, 77
 BLOOD, changes of, in old age, 411
 — degeneration, see *Leukæmia and pernicious anæmia*, 381
 — — molecular, 385
 — disorders, 363
 — functions of, 366
 — infantilism of, see *Anæmia, aplastic*, 379
 — normal structure of, 365
 — overgrowth of, 371; see *Chlorosis*.
 — red, system, functions of, 366
 — — — infantilism of 379; see *Anæmia, aplastic*.
 — — — overgrowth of 368; see *Polycythæmia*.
 — — — senilism of, 380; see *Anæmia, pernicious*.
 — white, system, overgrowth of, 370; see *Leucocytosis*.
 — — — pathology of, 383
 — — — physiology of, 383
 — — — senilism of, 381; see *Leukæmia*.
 BLOOD-CRISES in pernicious anæmia, 388
 BLOOD-ORGANS, disorders of, 380

- BONE, degeneration, 440; see *Osteitis deformans*.
 — development of, 417
 — — at puberty, 457
 — disorders of, 416
 — fibrous metaplasia of, 442
 — fragility of, 430
 — growth, relation to sexual organs, 457
 — — in achondroplasia, 425
 — — in giant hand, 236
 — — in osteitis deformans, 446
 — — in osteogenesis imperfecta, 430
 — — in osteomalacia, 446
 — — in rickets, 421, 423
 — overgrowth, 420, 424; see *Rickets* and *Achondroplasia*.
 BONE-MARROW, degeneration of; see *Osteomalacia*, 391
 BORUWLASKI, Joseph, an ateleiosic dwarf, 593
 BRACHYCEPHALY in ateleiosis, 595
 — in prehistoric man, 621
 BRAIN, convolutions of, in mongolism, 582
 — defects of, 93
 — — causes of, 316
 — — in amaurotic family idiocy, 326
 — — in microcephaly, 325
 — degeneration of, consecutive to infantilism, 314, 325; see *Insanity*.
 — dwarfism of, 322
 — effect of lead on, 75
 — — of alcohol on, 75
 — in childhood, degenerations of, 325
 — overgrowth of, 321
 — — partial, of, 321
 — shrinkage of, in senility, 320
 — undergrowth of, 322
 — weights of overgrown, 321
 BREAST, adenomatosis of, 258
 — cancer of, 157, 158, 179, 186, 191, 256
 — — causes of, 166
 — — course of, 168
 — — heredity in, 165
 — — ovariectomy for, 179
 — — sex in, 9
 — — symmetrical, 194
 — — X rays in, 175
 — cystic disease of, 260
 — — — anatomy of, 260
 — — — associations of, 260
 — — — treatment of, 260
 — degenerative hyperplasia of, 257
 — — — age in, 257
 — — — anatomy of, 258
 — — — associations of, 258
 — — — causes of, 257
 — — — course of, 257
 — — — nutrition in, 258
 — — — prognosis of, 258
 — — — treatment of, 259
 — — hypoplasia of, 259
 — development, defective, of, 181, 255, 540
 — disorders of, 255
 BREAST, fibro-adenomata of, 256
 — — fibromatosis of, 258
 — — giant, 257; see *Breast, degenerative hyperplasia of*.
 — — hypertrophy of, 256
 — — infantilism of, 255
 — — male, enlarged, 535, 537
 — — — in obesity, 507
 — — misplaced, 181
 — — overgrowth of, 256
 — — senilism of, 257
 — — supernumerary, 256, 259
 — — undergrowth of, 255
 BRIGHT'S disease, 299, 302
 — — acute, 301
 — — age in, 300, 309
 — — alcohol as cause of, 304
 — — anatomy of, 310
 — — associated with arterial sclerosis, 308
 — — — with general paralysis, 331
 — — — with hyperplasia of gums, 298
 — — — with kidney malformation, 298
 — — — with liver cirrhosis, 279
 — — — with obesity, 515
 — — — with osteomalacia, 449
 — — — with pancreatic disease, 308
 — — — with pernicious anæmia, 398
 — — associations of, 309
 — — caused by alcohol, 304
 — — — by gout, 304
 — — — by lead, 304
 — — — by pregnancy, 305
 — — — by scarlet fever, 304
 — — — by syphilis, 304
 — — — by toxins, 304
 — — causes of, 304
 — — of children, 296
 — — consecutive to infantilism of kidney, 303
 — — — course of, 300, 309
 — — — definition of, 302
 — — — diet in, 313
 — — — differentiation from nephritis, 301
 — — — effect of climate on, 313
 — — — of exercise on, 313
 — — — of operation on, 273
 — — in fœtus, 304
 — — heredity in, 307
 — — in infancy, 296
 — — inflammation in, 301
 — — large white kidney of, 301
 — — liver cirrhosis, comparison with, 299, 312
 — — — nephritis in, 302
 — — — pathology of, 310
 — — — in pregnancy, 305
 — — — Rose Bradford's variety of, 303
 — — — scarlet fever as cause of, 304
 — — — in single kidney, 294
 — — — small white kidney of, 303
 — — — — structure of, 300
 — — — syphilis as cause of, 304
 — — — treatment of, 313

- BRIGHT'S disease, unilateral, 297
 — — as variation, 105, 107
 — — varieties of, 300
- CALCULI, biliary, in liver cirrhosis, 281
- CANCER, 133, 153
 — aetiology of, 166
 — age-incidence of, 196
 — anatomy of, 184
 — arsenic as cause of, 162
 — — in treatment of, 178
 — bacterial toxins in, 173
 — beginning of, 193
 — bilateral, 190
 — biology of, 210
 — of breast, 179, 256; see *Breast, cancer of*.
 — castration in, 180
 — causes of, 160
 — cells, 133, 194
 — — amoeboid, 209
 — — functioning, 194
 — in Ceylon, 167
 — chimney sweeps', 111
 — clinical characters of, 55, 160
 — Cohnheim's theory of, 193
 — Coley's fluid in, 179
 — in the colonies, 166
 — a compromise, 208
 — course of, 167
 — — a degeneration, local, 53, 55, 190
 — — a developmental change, 194
 — erysipelas and, 174
 — excision of, 172
 — heredity in, 163, 164
 — inoculation in, 173
 — inoperable, 173
 — — caustics in, 173
 — — X rays in, 176
 — intermediate, 197
 — — with degenerated organs, 204
 — — with innocent tumours, 198
 — intermittency of, 168
 — in invertebrates, 167
 — leucocytes in, 184
 — in liver cirrhosis, 291
 — malignancy of, 185, 197
 — multiple, 190
 — nature of, 54, 173, 208
 — nerve distribution, 205
 — in old age, 135, 158
 — origin of, 192, 208
 — — in liver cirrhosis, 292
 — ovaries, removal of, in, 179
 — pathology of, 187, 190, 208
 — of penis, 161
 — of pituitary body, 668
 — pre-cancerous stages of, 188
 — predisposing conditions to, 207
 — pregnancy, effect of, on, 165
 — process, 185
 — prognosis of, 55, 171
 — proliferation in, 186
 — racial origin of, 166
- CANCER, radium in, 175
 — of rectum, 344
 — relation of, to benign growths, 182
 — — to degeneration of organs, 183, 187
 — — to eczema of nipple, 184
 — — to fibromyomata, 183
 — — to Hodgkin's disease, 404
 — — to hyperplasia of stomach, 343
 — — to leukaemia, 408
 — — to malformations, 181
 — — to old age, 187, 190, 195
 — — to osteitis deformans, 451
 — — to osteomalacia, 451
 — — to pernicious anaemia, 403
 — — to pre-natal malformation, 181
 — — to sex precocity, 182
 — rests, embryonic, in, 152, 182, 188, 193
 — — "post-natal" in, 188
 — a reversion, 194, 196
 — Ribbert's theory of, 193
 — in savages, 167
 — senilism in, 194
 — senility in, 195
 — sex in, 165
 — sources of, 142
 — spontaneous improvement in, 169, 174
 — of stomach, 166, 190, 343
 — structure of, 192
 — transformation of gland-cells into, 184
 — traumatic origin of, 161
 — treatment of, 171
 — in United States, 167
 — a variation, 210
 — varieties of, 134, 142
 — X rays in, 175
 — in youth, 135, 158, 210
 — zoological distribution of, 166
- CARCINOMA associated with other degenerations, 72
 — — with sarcoma, 157; see also *Cancer*.
- CARCINOMATOSIS, 190
- CARNARO, Luigi, a centenarian, 35
- CARTILAGE in achondroplasia, 425
 — in acromegaly, 671
 — development of, 417
 — functions of, 417
 — "rests," 417
- CASTRATION, effect on female, 480
 — — on male, 480, 534
 — in cancer, 183
- CAUSTICS in inoperable cancer, 173
- CELLS, adaptation of, to environment, 109
 — brain, 117
 — — in insanity, 320
 — cartilage, hyperplasia of, 422
 — — in achondroplasia, 425
 — — in bone formation, 422
 — collective action of, 27
 — connective-tissue, 185
 — — degeneration of, 81
 — defective growth of, 39
 — degeneration of, 18, 79, 86, 133, 136, 363
 — derived phylogenetically from cells, 26

- CELLS, development of, 18
 — epithelial, in Bright's disease, 312
 — — in endometritis, 361
 — fat, degeneration of, 505
 — gland-, in hyperplasia of breast, 259
 — growth of, 79
 — infantilism of, 152
 — "inflammatory," 81
 — liver-, in atrophic cirrhosis, 283
 — — in biliary cirrhosis, 284
 — molecular degeneration of, 86
 — motor, degeneration of, 315
 — nerve-, in amaurotic family idiocy, 326
 — — in general paralysis, 333
 — non-phagocytic, 21
 — overgrowth of, 39, 147, 149
 — plant-, in marine worms, 113
 — polymorphonuclear, functions of, 81
 — primitive volition of, 27
 — proliferation of, 43
 — retrogression of, 19
 — senilism of, 43, 111, 153
 — — varieties of, 154
 — senility of, 18
 — sex, 117
 — — effect of alcohol on, 77
 — — — of syphilis on, 77
 — undergrowth of, 39, 147
 — "rests," 152, 182
- CENTENARIANISM, 472, 542
 — effect of environment on, 544
 — examples of, 544, 545
 — frequency of, 543
 — heredity of, 102, 543
 — as a variation, 546
- CEREBRUM, defective development of, 323
- CEREBRO-SPINAL infantilism, 571
- CHANG, a giant, 492
- CHANGES of life, 31, 114
- CHILDHOOD, 31
 — Bright's disease of, 296
 — cirrheses of, 270
- CHILDBIRTH, an exaggerated menstruation, 34
- CHIQUITA, an ateleiosic dwarf, 587
- CHLOROMA, 409
- CHLOROSIS (overgrowth of blood), 371
 — arsenic in, 374
 — associated with anomalies of growth, 372
 — — with arterial infantilism, 348
 — — with kidney infantilism, 372
 — — with obesity, 515
 — — with sex infantilism, 348
 — — — precocity, 527, 530
 — blood volume in, 371
 — caused by arterial hypoplasia, 348
 — causes of, 373
 — causing obesity, 513
 — sex in, 372
 — spontaneous disappearance of, 372
 — symptoms of, 373
 — varieties of, 374
- CHORION-EPITHELIOMA, 182
- CHORION-EPITHELIOMA, origin of, 156
- CLEIDO-CRANIAL dysostosis, 419, 438
 — associations of, 439
 — heredity in, 438
- CLIMACTERICS, 31, 145
 — effect of, on developmental disorder, 44
- CLITORIS, enlarged, in senilism, 665
 — — in sexual precocity, 527
- COLON, degenerative hyperplasia of, 343
 — giant growth of, 343
- CORRELATION, 93, 476
 — familial, 96
 — in disease, 477, 481
- CORRELATIVE infantilism, 567
 — senilism, 627, 634
- CRACHAM, Caroline, an ateleiosic dwarf, 580, 599
- CRATERUS, a case of general senilism, 635
- CRETINISM, 624
 — a secondary infantilism, 626
 — associated with achondroplasia, 429
 — atavistic features of, 626
 — causes of, 483
 — treatment of, 624
 — a variation, 626
- CRIMINALS, as variations, 101
- CRYPTORCHISM in ateleiosis, 601, 605, 606, 608
 — in mongolism, 582, 583
- DEATH, natural, 20
- DEGENERATES, 90, 91, 92
- DEGENERATION, 60
 — alcohol as cause of, 65, 67, 209
 — arterial, 346
 — association with genius, 92
 — causes of, 60, 70
 — characters of, 83
 — definition of, 85
 — effect of environment on, 111
 — — of habit on, 73
 — — of locality on, 73
 — — of migration on, 73
 — — of race on, 73
 — fibrous, 261
 — — in arterial disease, 349
 — general, 634, 637
 — influence of heredity on, 71
 — malignant, 142
 — molecular, 43, 86, 385
 — nature of, 80
 — of blood, 381
 — of bone-marrow, 391
 — of brain, 83, 314, 325
 — of breast, 257
 — of cells, 79, 133, 363
 — of colon, 343
 — of extremities, 218
 — of foetus, 156
 — of gastro-intestinal tract, 335
 — of glands, 134
 — of intestines, 343
 — of joints, 462

- DEGENERATION of kidney, 299
 — of liver, 263
 — of lymphatic system, 204
 — of Malpighian bodies, 390
 — of motor cells, 315
 — of muscle, 246, 341
 — of nervous system, 314
 — of organs, 80, 104, 133
 — — relation of cancer to, 183
 — of skeleton, 440
 — of thyroid gland, 643
 — of uterus, 359
 — pregnancy as cause of, 70
 — prosenchymatous, 261
 — racial, 86
 — reversion in, 43
 — senile, 82, 86
 — stigmata of, 89
 DEMENTIA paralytica, 332
 — — arterial sclerosis in, 333
 — præcox, 326
 — — characters of, 327
 — — heredity in, 327
 — — nature of, 327
 — — symptoms of, 327, 328
 — — types of, 328
 DENTITION in ateleiosis, 591, 599, 603, 608
 — in mongolism, 582
 — in progeria, 651
 — in senilism of mixed origin, 641
 DEPRESSION a cause of disorders, 59
 DEVELOPMENT, adaptation of, normal, 109, 474
 — — in disease, 479
 — correlation of, normal, 93, 474
 — — in disease, 479
 — defective, 42
 — disorders of, structural changes in, 79, 136
 — effect of gluttony on, 35
 — errors of, 74
 — extremes of, 39
 — growth and nutrition, 10, 11, 38
 — interruptions of, 31
 — of kidney, defective, 294
 — normal, 11
 — — climacterics of, 31, 44
 — — decline of, 29
 — — and degeneration, 13
 — — of hardship on, 36
 — — of insanitation on, 63
 — — of privation on, 35
 — — of tobacco on, 561
 — — epochs of, 31
 — — of organs, definition of, 57
 — — ontogenetic, 12
 — — phylogenetic, 12
 — pre-natal and post-natal, relations between, 74
 — — rate of, 30
 — — rise of, 29
 — — stages of, 31
 — — a variable process, 30
 DEVELOPMENT, premature, see *Sexual precocity*, 42, 521
 — regressive, acceleration of, see *Senilism*, 627
 — retarded or hastened by circumstances, 35
 — senile, 14
 DIABETES associated with acromegaly, 667
 — — with liver cirrhosis, 282
 — — with obesity, 504, 515
 — — with senilism, 664, 665
 DIARRHŒA in infantilism, 561
 DIET in arthritis deformans, 465
 — in Bright's disease, 313
 — in obesity, 516
 DI-HYBRIDISM, 128
 DILATATION, operative, of pylorus, 339
 DISEASE, associations of, 72
 — effect of environment upon, 105
 — of extrinsic origin, 46
 — — — nature of, 46
 — of intrinsic origin, 51
 — of mixed intrinsic and extrinsic origin, 55
 — nature of, 45
 DISSEMINATED sclerosis, 334
 — — heredity of, 334
 DOLICOCEPHALY in infantilism, 567
 DRUGS, effects of, on fœtus, 74
 — equivalent to toxins, 48
 DWARFISM, characters of, 486
 — definition of, 488
 — ontogenetic, 485
 — phylogenetic, 485
 — racial, 42, 485, 552
 — varieties of, 485
 DWARFS, ateleiotic, 586
 — "Aztec," 574
 — court, 588
 — imbecile, 573
 — intelligent, 576
 — longevity of, 629
 — microcephalic, 573
 — skeleton of a, at Cambridge, 42
 DYSOSTOSIS, cleido-cranial, 438
 EDWARDS, Millie, a microcephalic dwarf, 577
 ELEPHANTIASIS, 223
 — "hereditary," 225
 — non-filarial, 224
 — tropical, 224
 — varieties of, 223
 ELEPHANTOID fever, 228
 EMACIATION, 503
 — muscular, 246, 649, 659
 EMBRYONIC characters, re-appearance of, in old age, 19
 EMOTION, toxic effect of violent, 46, 317
 ENDOMETRITIS, cells in, 361
 — chronica cystica, 362
 — glands in, 361

- ENDOTHELIOMA** associated with liver cirrhosis, 293
 — in Hodgkin's disease, 410
 — in splenic anæmia, 391, 410
 — of carotid bodies, 153
 — of lymph-glands, 405
 — of spleen, 405
ENVIRONMENT, adaptation of cells to, 474
 — — lower animals to, 475
 — — man to, 475
 — definition of, 109
 — depressing, causing infantilism, 547, 559
 — — — nervous disease, 333
 — — causing senilism, 632
 — — effect of, on longevity, 545
 — effect of, on arthritis deformans, 465
 — — on the body, 111
 — — on chlorosis, 373
 — — on development, 29
 — — on feminism, 536
 — — on insanity, 317
 — — on leukæmia, 389
 — — on organs, 111
 — — on pernicious anæmia, 389
 — — on sex characters, 539
 — favourable, causing longevity, 542
 — "internal," 138
EPILEPSY, a rhythmic disorder, 123
EPITHELIOMA, trabéculaire, 292
 — varieties of, 158
EPULIS, 232
EPOCHS of life, effect on disease, 44
ERYSIPELAS, effect of, on cancer, 174
EUTHANASIA, mechanism of, 20
EVERITT, Thomas Hill, a giant child, 499
EVOLUTION, 118
EVOLUTIONARY infantilism (general), 547
 — senilism (general), 629
EXERCISE in arterial disease, 353
 — in Bright's disease, 313
 — in obesity, 516
EXTREMITIES, defective development of, relation to degenerative hyperplasia, 238
 — degeneration of, 218
 — degenerative hyperplasia of, 219, 220
 — — ætiology of, 222
 — — age in, 223
 — — amputation in, 230
 — — arterial sclerosis in, 234
 — — associations of, 231
 — — clinical characters of, 222
 — — complications of, 227
 — — correlation in, 239
 — — course of, 226
 — — diagnosis of, 223
 — — heredity in, 225
 — — inflammation in, 227, 230
 — — osteomalacic changes in, 237
 — — pathology of, 235
 — — phagocytosis in, 235
EXTREMITIES, degenerative hyperplasia of, recurrence of, 230
 — — relation to defective development, 238
 — — — to nervous system, 239
 — — remittent, 226
 — — results of, 229
 — — sex in, 223
 — — structure of, 232
 — — treatment of, 229
 — — — by compression, 229
 — — ulceration in, 228, 237
 — — varieties of, 220
 — disorders of, 218
 — hyperplasia of, 219
 — infantilism of, 231
 — overgrowth of, 219
 — — nature of, 219
 — — relation to degeneration, 219
 — — results of, 227
EXTRINSIC diseases, 46

FACE, disproportion of, 90
FACIAL hemiatrophy, 239
 — hemi-hyperplasia, 239
FEAR, ageing effects of, 35
FEMINISM, 473, 534
 — acromegalic, 539, 673
 — associated with acromegaly, 537
 — — with gigantism, 539
 — — with obesity, 537
 — characters of, 435
 — effect of environment on, 536
 — heredity in, 537
 — obesity in, 502
 — racial, 539
 — a variation, 536
FENWICK, Bobbie, an infantile dwarf, 606
FERRY, Nicholas, a case of general senilism, see *Bébé*, 637
FEVER in chlorosis, 373
 — in giant breast, 257
 — in leukæmia, 389
 — in myositis ossificans, 253
 — in pernicious anæmia, 389
 — infectious, causing acromegaly, 666
 — — — pre-natal deformity, 74
 — — — infantilism, 559
 — — — senilism, 633
 — rheumatic, causing infantilism, 560
 — scarlet, causing Bright's disease, 304
FIBROBLASTS, see *Cells*, 81
FIBROID, recurrent, a mixed growth and degeneration, 198
FIBRO-MYOMATA in degenerative hyperplasia of uterus, 360
 — relations with cancer, 183
FIBROSIS, arterial, 348
 — cerebro-spinal, 318
 — in Hodgkin's disease, 407
 — of heart, 370
 — of kidney, see *Bright's disease*, 298

- FIBROSIS of liver, see *Liver cirrhosis*, 265
 — of lungs, 402
 — of pituitary body, 668
 — of spleen, 390
 FIBROUS degeneration, 261
 — — pathology of, 364
 FILARIA sanguinis hominis, 223
 FLUCTUATIONS, 100
 FLYNN, Frank, a microcephalic dwarf, 577
 FŒTUS, ateleiosis of, 599
 — Bright's disease of, 304
 — effects of drugs on, 74
 — — of toxins on, 51
 — largest known, 490
 — malformations of, 51, 582
 — nutrition of, 51
 FONTANELLE, premature closure of, in progeria, 662
 — unclosed in mongolism, 582
 — — in senilism, 651
 FORBES, Archibald, effect of hardship on, 632
 FRAGILITAS ossium, see *Osteogenesis imperfecta*, 433
 FREEMAN, a giant, 488
 FRIEDREICH'S ataxia, 326
 — — associated with idiocy, 326
 — — — with precocious obesity, 509
 — — a consecutive degeneration, 326
 GALACTORRŒA in acromegaly, 671
 GALL-STONES in cirrhosis, 281
 GAMETES, 126
 GASTRO-INTESTINAL tract, cancer of, 165
 — — disorders of, 325
 GATH, giant of, 493
 GENERAL paralysis, 328
 — — age in, 330
 — — anatomy of, 332
 — — a reversion, 332
 — — associated with Bright's disease, 331
 — — — with malformations, 331
 — — — with tabes dorsalis, 331
 — — associations of, 331
 — — caused by alcohol, 330
 — — — by civilisation, 329
 — — — by excesses, 329
 — — — by lead, 330
 — — — by overwork, 329
 — — — by shock, 330
 — — — by syphilisation, 329
 — — causes of, 329
 — — comparison of, with liver cirrhosis, 333
 — — course of, 329
 — — effect of pregnancy on, 330
 — — pathology of, 332
 — — phagocytosis in, 333
 GENITAL organs, defective development of;
 see *Sexual development, defective*, 502,
 506, 589
 GENIUS associated with degeneracy, 92
 — — with obesity, 509
 GENIUS, nature of, 101
 — relation to talent, 100
 GIANTS, children, 491
 — of Stone Age, 618
 — records of, 492; see also *Gigantism*,
generat.
 GIANT extremities; see *Extremities, de-*
generative hyperplasia of, 218
 — hand, 234; see *Extremities, degenerative*
hyperplasia of.
 — — age in, 223
 — — associations of, 231
 — — cause of, 222
 — — pathology of, 237
 — — sex in, 223
 — — structure of, 233
 — — treatment of, 229
 GIBRALTAR skull, 618
 GIGANTISM, general, 41, 487
 — — adult, associated with acromegaly,
 678
 — — — — with feminism, 539
 — — — — with local disorders, 494
 — — — — with lymphatism, 495
 — — — — with obesity, 509
 — — — — with polydactylism, 493
 — — character of, 488
 — — comparison with acromegaly, 489
 — — complicated, 494
 — — correlated, 494
 — — pituitary body in, 488
 — — prepubic, 489, 495
 — — relation to local gigantism, 490
 — — varieties of, 487, 489, 495
 — infantile, 495
 — local; see *Extremities, degenerative*
hyperplasia of, 221
 — — precocious, 489, 495
 — — associated with lymphatism, 495
 — — dentition in, 497
 — — hair in, 497
 — — intelligence in, 498
 — — muscular strength in, 497
 — — relation to feminism, 490
 — — — to masculinism, 490
 — — sexual system in, 498
 — — voice in, 497
 GIN, effect of, on growth, 564
 GIROMORPHISME cutané, 665
 GLANDS, lymph-, cancer of, 405
 — — diseases of, 405
 — — effect of irritation on, 377
 — — endothelioma of, 405
 — — enlargement of, 282
 — — Hodgkin's disease of; see *Hodgkin's*
disease, 389, 407
 — — overgrowth of, 377
 — — sarcoma of, 377, 406
 — — structure of, 133
 — mammary, 255
 — — congenital absence of, 646
 — sex, defective action of, 513
 — stomach, atrophy of, 342

- GLANDS, thymus, function of, 375
 — thyroid, infantilism of, 467, 624
 — — senilism of, 467, 643
 GLIOMA, congenital, 159
 GLUTTONY, effect of, on development, 35
 GOITRE, in acromegaly, 667
 — in ateleiosis, 608, 612
 — in gigantism, 492
 — in Graves's disease, 467
 — parenchymatous, 467
 — — cause of, 357
 — — effect of operation on, 273; see also *Graves's disease*.
 GOLIATH, 493
 GORILLA, comparison with acromegaly, 676
 GOUT, associated with obesity, 515
 — causing arterial disease, 347, 350
 — — Bright's disease, 304
 — — hyperplasia of stomach, 339
 — — senilism, 633
 GRANULATION-TISSUE, relation to cancer, 198
 — tumours, 198
 GRANULOMA, 197
 — digital, innocent, 200
 — — malignant, 201
 — — semi-malignant, 200
 — fungoides, 203
 — malignant, 156
 — multiple, 203
 — — treatment of, 204
 — of nasal septum, 199
 — of vermiform appendix, 202
 — semi-malignant, 202
 GRAVES'S disease, 376, 467
 GROWING pains of acromegaly, 668
 — — of childhood and adolescence, 32
 — — of pregnancy, 32
 GROWTH, adaptation in disease, 477
 — — normal, 474
 — — comparison with development, 11
 — control of, 24
 — defective, 39
 — development and nutrition combined normally, 9
 — — — separated in disease, 38
 — disorders associated with sterility, 358
 — — structural changes in, 57, 79
 — excessive, 39
 — giant, 218
 — reproductive, 10
 — somatic, 10
 GUMS, hyperplasia of, associated with Bright's disease, 298
 — — general infantilism, 231
 GRIEF, ageing effect of, 35
 GYNÆCOMASTIA, 257
 — in effeminate races, 539
 — in obesity, 507
 — unilateral, 535
 HABIT as cause of degeneration, 37
 — as rhythm, 122
 HAIR, absence of, pre-natal, 646
 — — in progeria, 649, 655, 657, 660
 — colour change in liver cirrhosis, 274, 634
 — — in microcephaly, 324
 — — in prehistoric man, 324
 — growth of, in ateleiosis, 606
 — — in dwarf races, 555
 — — in obesity, 503
 — — in old age, 475
 — — in precocious gigantism, 497
 — — in prehistoric man, 622
 — loss of, in myxœdema, 643
 — — seasonal, 113
 — sexual, absence of, 569
 — — associated with dental malformation, 540
 — — — with masculinism, 540, 673
 — — — with sexual precocity, 405, 636
 HALE, Robert, a giant, 42
 HALL, Thomas, a case of general senilism, 636
 HAMPOLE on old age, 14
 HAND, giant, see *Giant hand*, 234
 HARDSHIP, effect of, on development, 36
 HEAD circumference in ateleiosis, 603, 606
 — — in microcephaly, 575, 576, 578
 — — in progeria, 655, 658
 HEART, congenital disease in Mongolism, 582
 — fibrosis of, in polycythæmia, 370
 — in pregnancy, 306
 — in progeria, 652, 655
 — in secondary senilism, 665
 HEMI-ATROPHY of face, 239
 HEMI-HYPERTROPHY of face, 221, 239
 HEREDITARY elephantiasis, 225
 — œdema, 225, 243
 — psychoses, 78
 HEREDITY, 29, 123, 125
 — familial, 71
 — importance of, 129
 — in achondroplasia, 429
 — in acromegaly, 667
 — in acute yellow atrophy of liver, 279
 — in albuminuria, 308
 — in alcoholism, 124
 — in arterial disease, 352
 — in ateleiosis, 593, 596
 — in blood diseases, 395
 — in Bright's disease, 307
 — in cancer, 163
 — in centenarianism, 543
 — in cirrhosis, 270, 271
 — in cleido-cranial dysostosis, 438
 — in degeneration, 70
 — in disseminated sclerosis, 334
 — in feminism, 537
 — in general obesity, 511
 — in giant extremities, 225
 — in idiocy, 333
 — in jaundice, 279
 — in longevity, 29, 542

- HEREDITY in microcephaly, 324
 — in muscular dystrophy, 248
 — in myositis ossificans, 252
 — in nervous diseases, 333
 — in osteitis deformans, 455
 — in osteogenesis imperfecta, 434
 — in osteomalacia, 454
 — in paralysis agitans, 334
 — in pernicious anemia, 395
 — in pre-natal malformations, 53
 — in sexual precocity, 528
 — in splenic anemia, 396
 — in tubercular disease, 124
 — in variations, 135
 — indirect, 71
 — influence on degeneration, 71
 — irregular, 129
 — transforming, 71, 129, 396, 537, 667
 HERMAPHRODISM, 502, 531
 — associated with defective thyroid gland, 72
 — partial, 527
 — in sexual precocity, 402, 526
 — post-natal, 502, 527, 531
 — pre-natal, 541
 HIRSUTIES in masculinism, 540
 — in obesity, 509
 — in sex precocity, 529
 HODGKIN'S disease, 389
 — — age in, 393
 — — associated with bone degeneration, 401, 448
 — — — with osteitis deformans, 401, 447
 — — — with osteomalacia, 402, 447
 — — — with pernicious anemia, 72
 — — course of, 394
 — — endothelioma in, 410
 — — heredity in, 395
 — — — transforming, 72
 — — histology of, 391, 407
 — — relations with cancer, 404
 — — — with osteomalacia, 447
 — — resemblance to splenic anemia, 389
 — — structure of, 407
 — — varieties of, 391
 HOPKINS, Hopkin, a case of (?) progeria, 659
 HUDSON, Jeffrey, an ateleiosic dwarf, 608
 HUMAN body, tribasic structure of, 26
 HUNTINGDON'S chorea, a consecutive senilism, 326
 HYDATIDIFORM mole, 156
 HYPERMYOTROPHY, see *Arterial overgrowth*, 347
 HYPERNEPHROMA associated with precocious obesity, 509
 — — with sex precocity, 578
 HYPERPLASIA, 487
 — definition of, 216
 — — degenerative, 80, 185, 217
 — — of arterial system, 348
 — — of blood, 392
 — — of breast, 257
 — — of colon, 343
 — — of extremities, 219
 — — of gums, 231, 298
 — — of kidney, 301
 — — of liver, 265
 — — of muscle, 246
 — — of organs, 132
 — — of man, 487
 — — of pylorus, 338
 — of stomach, anatomy of, 341
 — — degenerative, see *Stomach, degenerative hyperplasia*, 337
 — of uterus, see *Uterus*, 359
 — varieties of, 216
 HYPERTROPHY, definition of, 80, 216
 — of kidney, 298
 — of limbs, 219
 — of liver, 284
 — of pituitary body, 668
 — of pylorus, 337
 — of red blood system, 368
 — of viscera, 41; see also *Overgrowth*.
 HYPOPLASIA, degenerative, of arteries, 348
 — — of breasts, 259
 — — of liver, 265
 — — of stomach, 243
 — — of uterus, 362
 HYPO-PITUITARISM, 670
 — glycosuria in, 670
 ICHTHYOSIS, 183
 ICTERUS albus, see *Chlorosis*, 393
 — gravis, see *Liver, acute yellow atrophy of*, 276
 IDIOCY, amaurotic family, 325
 — — — anatomy of, 326
 — microcephalic, 573
 — mongol, 580
 IMBECILITY associated with infantilism, 571
 — microcephalic, 573
 — mongol, 580
 IMMUNITY, 9
 — depressed, 50
 — — by alcohol, 50, 69
 — — in obesity, 515
 INFANTILE progeria, 660
 INFANTILISM, 87, 144
 — alcoholic, 563
 — biology of, 146
 — cerebro-spinal, 323
 — definition of, 87
 — essential, 585.
 — general, 472, 547
 — — adaptative, 558
 — — alcohol as cause of, 483, 548, 563
 — — anangioplasic, 568
 — — arterial, 348, 550, 568
 — — associated with acromegaly, 673
 — — — with defective intelligence, 571
 — — — with hydrocephalus, 571
 — — — with hyperplasia of gums, 231

- INFANTILISM, general, associated with hypertrophic cirrhosis, 567
- — — with imbecility, 571
 - — — with microcephaly, 572
 - — — with muscular dystrophy, 567
 - — — with obesity, 508
 - — — with osteogenesis imperfecta, 437
 - — — with Pott's disease, 566
 - — — with Raynaud's disease, 569
 - — — with scleroderma, 567
 - — — with senilism, 616
 - — — with splenomegaly, 567
 - — Brissaud's type of, 549
 - — — combined with Lorain's type, 583
 - — cardiac, 568
 - — causes of, 481, 547
 - — causes often obscure, 482
 - — cerebro-spinal, 571
 - — classification of, 550
 - — correlative, 566
 - — course of, 615
 - — cretinism, 483, 624
 - — debility a cause of, 482
 - — defective nutrition a cause of, 481
 - — degeneration a cause of, 481
 - — developmental, 557
 - — — environment as cause of, 111, 547
 - — — insanitation as cause of, 558
 - — evolutionary, 547, 551
 - — hepatic, 567
 - — indeterminate, 583
 - — infective fever as cause of, 559
 - — intestinal, 561, 584
 - — Lorain's type of, 549
 - — — combined with Brissaud's type of, 583
 - — microcephalic, 572
 - — mitral, 568
 - — mixed causes of, 583
 - — mongol, 582
 - — myxœdematous type of, 549
 - — neuropathic, 571
 - — of insanitation, 558
 - — of membrane formed bone, 438
 - — of mixed origin, 564
 - — pancreatic, 483, 562, 584
 - — pituitary body in, 681
 - — prognosis, 615
 - — racial, 551
 - — — historical account of, 555
 - — — resemblance to children, 553, 554
 - — — simian features of, 553
 - — relations of, 76
 - — rheumatic fever as cause of, 560
 - — senilism simultaneous with, 464
 - — sexual, 582
 - — symptomatic, 548, 557, 559
 - — — adaptation in, 557
 - — — classification in, 557
 - — — correlation in, 557
 - — syphilis as cause of, 483, 564
 - — thyroid in, 550, 624
 - — tobacco as cause of, 560, 561
- INFANTILISM, general, toxins as cause of, 483
- — toxic, 559, 599
 - — types of, 549
 - — of uterus, 357
 - — as a major variation, 549, 585
 - — as a minor variation, 548, 557
 - — varieties of, 587
 - of arteries, 348
 - of blood, 378
 - of bone, 430, 438
 - of brain, 323, 572
 - of breast, 255
 - of cells, 88, 142, 152
 - of kidneys, 291, 296
 - of liver, 216
 - of nervous system, 323
 - of organs, 88, 140
 - — of skeleton, 430, 438
 - — of spleen, 378, 567
 - — of stomach, 336
 - of thyroid gland, 467, 624
- INFLAMMATION, 82
- a defensive process, 82
 - in arthritis deformans, 465
 - in Bright's disease, 301
 - in macrosomia, 227, 230
 - of kidney, 301
 - of liver, 301
- INFLUENZA causing jaundice, 302
- — senilism, 633
 - in a centenarian, 545
- INSANITATION, causing infantilism, 558
- — senilism, 632
 - effect of, on development, 36
- INSANITY, adolescent, 327
- alcohol as cause of, 216
 - associations of, 319
 - brain-cells in, 320
 - causes of, 316
 - course of, 317
 - duration of, 319
 - effect of environment on, 317
 - lead as cause of, 316
 - of adolescence, 327
 - of menopause, 319
 - of pregnancy, 319
 - periodic, 317
 - prognosis of, 316
 - puerperal, 319
 - syphilis as cause of, 316
 - treatment of, 317
- INTELLIGENCE, defective, associated with general infantilism, 575
- INTESTINAL infantilism, 561
- INTESTINES, chronic infection of, 561
- hyperplasia, degenerative, of, 343
 - — — cancer in, 343
 - infantilism of, 584
 - in progeria, 652
- INTOXICATION, 49
- INTRINSIC origin of disease, 45
- IRRITATION causing cancer, 161

- IRRITATION causing cirrhosis, 269
 — — new growths, 150
 — effect on lymph-glands, 377
- JENSEN'S mouse tumour, 203
- JOINTS, 417
 — degeneration of, see *Arthritis deformans*, 462
 — senilism of, see *Arthritis deformans*, 462
- KAHLER'S disease, 448, 453
- KIDNEY, atrophy of, associated with general infantilism, 296
 — — causing fatal uræmia, 297
 — Bright's disease of, see *Bright's disease*, 299
 — defective development of, see *Kidney infantilism*, 294
 — disorders of growth and development of, 294
 — fibrosis of, see *Bright's disease*, 299
 — granular, see *Bright's disease*, 299
 — infantilism of, 294
 — — associated with cancer, 295
 — — — with chlorosis, 372
 — — Bright's disease secondary to, 295, 303
 — in Bright's disease of early infancy, 296
 — large white, see *Bright's disease*, 299
 — misplaced, 298, 402
 — senilism of, see *Bright's disease*, 299, 303
 — single, 294
 — small white, of Rose Bradford, 293 ; see also *Bright's disease*.
- KIMOS, 552
- LACTATION, decline of nutrition in, 33
 — facilitating arthritis deformans, 464
 — — leukemia, 389
 — — pernicious anæmia, 389
- LAMBERT, Daniel, a case of obesity, 508
- LAVATER, description of ateleiosis, 588
- LEAD and alcohol, reciprocity between, 67
 — causing abortion, 77
 — — acromegaly, 666
 — — Bright's disease, 304
 — — degeneration, 62
 — — general paralysis, 330
 — — insanity, 316
 — — liver cirrhosis, 269
 — — muscular dystrophy, 248
 — — pernicious anæmia, 393
 — — senilism, 633
 — — sterility, 77
 — combined with syphilis and alcohol, as cause of degeneration, 67
 — effects of, 62
 — — combined with alcohol, 67
 — — on brain, 75
 — — on fœtus, 75
 — — toxic, 61
 — as toxin, 62
- LEUCOCYTES associated with cancer, 185
 — in disease, 383
 — in health, 382
 — in leukemia, 383
 — in leukanæmia, 392
 — in polycythæmia, 369
 — in pregnancy, 33
 — molecular degeneration of, 385
- LEUCOCYTOSIS, 370
 — in appendicitis, 382
 — in septicæmia, 382
 — pathological, 371
 — physiological, 370
- LEUCOPENIA in aplastic anæmia, 379
- LEUKÆMIA, 383, 414
 — age in, 394
 — arsenic in, 389, 415
 — a sarcomatosis, 409
 — associated with Bright's disease, 402
 — — with cirrhosis, 282, 399
 — — with osteomalacia, 449
 — — with pre-natal malformations, 402
 — — with spinal sclerosis, 400
 — biology of, 415
 — causes of, 393
 — clinical characters of, 389, 415
 — course of, 394
 — effect of environment on, 389
 — — of lactation on, 389
 — — of pregnancy on, 389
 — evidences of degeneration in, 383, 385
 — heredity of, 395, 396
 — influenza as cause of, 393
 — in the lower animals, 396
 — malaria as cause of, 393
 — pathology of, 409, 415
 — pre-natal, 402
 — relations with cancer, 408
 — — with pernicious anæmia, 384, 388
 — remissions in, 395
 — resemblance to pernicious anæmia, 388
 — structural characters of, 392, 415
 — temperature in, 389
- LEUKANÆMIA, 392, 410
- LIFE, abnormal duration of, 542
 — normal, changes of, 31, 44, 145
 — — curtailed by hardship, 632
 — — duration of, 115, 543, 629
 — — in racial infantilism, 629
 — — stages of, 31; see also *Centenarianism*.
- LIPOMA, 150
 — diffuse, 502
- LIVER, adenomatosis of, 289
 — adenoma, of, 263
 — acute yellow atrophy of, 275
 — — — age in, 277
 — — — alcohol as cause of, 268
 — — — consecutive to cirrhosis, 278
 — — — effect of pregnancy on, 275
 — — — hereditary in, 279
 — — — illegitimate pregnancy as cause of, 277
 — — — origin of, 275

- LIVER, acute yellow atrophy of, resemblance to cirrhosis, 277
- — — sex in, 277
 - — — structural characters of, 277
 - — — toxins as cause of, 278
 - cirrhosis, 265
 - — acute, 267
 - — adenomatosis in, 290
 - — age in, 269
 - — alcohol as cause of, 68, 104, 268, 290
 - — anatomy of, 282
 - — arsenic as cause of, 269
 - — as a variation, 104, 287, 291
 - — associated with arterial sclerosis, 279
 - — — with Bright's disease, 279
 - — — with diabetes, 282
 - — — with endotheliomata, 293
 - — — with fibrosis of pancreas, 280
 - — — with general infantilism, 567
 - — — with large white kidney, 282
 - — — with pernicious anæmia, 397
 - — — with sarcomatosis, 293
 - — — with senile decay, 290
 - — — with senilism, general, 634
 - — atrophic, 282
 - — biliary, 284
 - — — comparison with atrophic variety, 286
 - — — heredity in, 271
 - — — new bile-ducts in, 286
 - — — proliferation of cells in, 284
 - — blocked bile-ducts in, 280
 - — carcinomatosa, 291
 - — causes of, 268
 - — cell proliferation in, 284, 289
 - — cell retrogression of, 19, 284
 - — comparison with Bright's disease, 299
 - — consecutive, 267
 - — course of, 267, 270, 272
 - — fibrosis in, 289
 - — heredity in, 269, 270
 - — in childhood, 270
 - — hypertrophic, see *Liver, cirrhosis, biliary*, 284
 - — irritation as cause of, 269
 - — jaundice in, 272
 - — lead as cause, 269
 - — malignant, 292
 - — obstructive, 281
 - — operation in, 273
 - — partial, 282
 - — pathology of, 282
 - — phagocytosis in, 82, 289
 - — portal, 282
 - — relation to acute yellow atrophy, 277
 - — — to cancer, 291
 - — remissions in, 272
 - — reversion in, 286
 - — sarcomatosis in, 293
 - — sex in, 269
 - cirrhosis, silver as cause of, 269
 - — structure of, 82, 288
 - — syphilitic, 267
 - — tight-lacing as cause of, 269
 - — treatment of, 272
 - — varieties of, 265, 266
 - — zoological distribution of, 269
 - defective development of, 263, 267
 - degeneration of, 263
 - hyperplasia of, 265
 - hypertrophy of, 284
 - hypoplasia of, 265
 - infantilism of, 263, 267
 - phylogeny, effect on pathology, 289
 - overgrowth of, 263
 - senilism of, see *Liver cirrhosis*, 265
 - undergrowth of, 263
- LOCOMOTOR ataxia, see *Tabes dorsalis*, 328
- LONGEVITY, abnormal, 542
- — a variation, 102
 - — heredity in, 544; see also *Centenarianism*.
 - normal, 20, 541, 629
- LOUIS II of Hungary, general senilism of, 635
- LUNAR changes, effect of, on rhythm, 114
- LUNGS, overgrowth of, 41
- LYMPHADENIA ossium, 447
- LYMPHADENOMA, see *Hodgkin's disease*, 389, 404
- LYMPHADENOMATOSIS of bone, 447
- LYMPHATIC anæmia, see *Hodgkin's disease*, 389, 404
- system, degeneration of, 381
- LYMPHATISM, 375
- associated with general gigantism, 495
- LYMPH GLANDS, degeneration of, see *Hodgkin's disease*, 389, 404
- endothelioma, 405
 - sarcoma of, 405
- LYMPHOCYTES, functions of, 81
- LYMPHOMATA, 377
- LYMPHOSARCOMA, 405
- MACRODACTYLY, see *Extremities, degenerative hyperplasia of*, 219
- MACROGLOSSIA, 230, 233
- MACROPHAGES, functions of, 20, 382
- — in osteomalacia, 445
- MACROSOMIA, general, see *Gigantism*, 487
- local, see *Extremities, degenerative hyperplasia of*, 219
- MAGDALENIAN stage of prehistoric man, 618
- MAGRI, "Baron," an ateleiosic dwarf, 387
- MALARIA causing leukæmia, 393
- causing senilism, 632
- MALE breast, enlargement of, 257
- MALFORMATIONS, 51
- pre-natal, associations, 53
 - — caused by toxins, 52
 - — causes of, 51
 - — clinical features of, 52

- MALFORMATIONS**, pre-natal, course of, 52
 — — endemic character of, 52
 — — in Mongolism, 582
 — — in osteogenesis imperfecta, 435
 — — pathology of, 52
 — — relations with cancer, 181
 — — transforming heredity in, 53, 72
 — relations of ante-natal to post-natal, 52
MALIGNANT tumours, see *Cancer*, 54, 133, 153
MALNUTRITION causing sterility, 77
MAMMITIS, chronic fibrous, see *Breast, senilism*, 257
MAN, prehistoric, 551, 618, 676
 — — brachycephaly in, 621
 — — characters of, 616, 678, 685
 — — evidences of, 618, 683
 — — hair of, 324, 622
 — — stages of, 618
 — — traditional evidence of, 622
 — — types of, 623, 683
 — adaptation of, 474
 — correlation of, 476
 — degenerative hyperplasia of, 494
 — disorders of, classification, 473
 — infantilism of, see *Infantilism, general*, 472, 547
 — overgrowth of, see *Gigantism*, 42, 487
 — undergrowth of, see *Dwarfism*, 472, 484
MANHOOD, 31
MASCULINISM, 473, 534, 540
 — associated with hermaphroditism, 541
 — — with senilism, 665
 — at menopause, 541
 — in acromegaly, 673
 — in obesity, 503
 — racial, 541
 — sexual organs in, 540
 — as variation, 541
 — varieties of, 540
MEMBRANE-FORMED bone, defective development of, 438
MEMORY, 115
 — racial, 115
MENDELISM, 125
MENOPAUSE, 114
 — chlorosis of, 374
 — insanity of, 319, 325
 — masculinism of, 541
 — nervous system, disorders at, 319
 — obesity of, 511, 514
 — origin of, 114
 — — of disease at, 44
 — relation of, to bone degeneration, 457
 — senilism of thyroid gland at, 468
MENORRHAGIA, in degenerative hyperplasia of uterus, 356, 359
MENSTRUATION, 32
 — a miniature childbirth, 33
 — affected by obesity, 514
 — — by overgrowth of uterus, 355
 — changes during, 33
MENSTRUATION delayed, 357
 — effect of, on arthritis deformans, 464
 — immunity increased before, 33
 — — lessened during, 33
 — origin in mensal periodicity, 114
 — precocious, 523, 530
 — — debilitating effect of, 530
 — protracted, 520
 — relations to childbirth, 34
 — rhythmic character of, 113
MENTAL deficiency, 334
 — — associated with deformity, 93
 — — heredity of, 334
 — — sterility in, 78
MICROCEPHALIC dwarfs, group of, 572
MICROCEPHALY, 322, 572
 — anatomy of, 325
 — associated with disseminated sclerosis, 324
 — — with infantilism, 572
 — — with muscular dystrophy, 324
 — — with simian characters, 573
 — associations of, 324
 — causes of, 324
 — circumference of head in, 575
 — correlation in, 479, 573
 — defective skull of, 324
 — degeneration consecutive to, 325
 — effect of age on, 325
 — forms of, 323
 — hair in, 324
 — heredity in, 324
 — infantilism in, 325
 — lead as cause of, 75
 — with intelligence, 575
MICROMEGLY, 682 : see also *Progeria*, 645
MICROPHAGES, 20, 282
MICROSOMIA, local, 41
 — general, 485
MIDDLE age, 31
MIGRAINE, a rhythmic disorder, 123
MIGRATION, effect on degeneration, 73
MILROY'S disease, 242
 — — as a variation, 243
 — — associations of, 243
 — — diagnosis of, 242
 — — inflammation in, 242
 — — symptoms of, 242
MINCOPIES (Andamanese), 552
MITE, "General," a microcephalic dwarf, 577
MITRAL infantilism, 568
MOLECULAR degeneration, 86
 — — of blood, 385
 — — of leucocytes, 385
MONGOLISM, 580
 — associations of, 582
 — associated with heart disease, 582
 — — with pre-natal malformation, 582
 — brain in, 582
 — causes of, 580
 — characters of, 580
 — dentition in, 582

- MONGOLISM, heart disease in, 582
 — ossification in, 582
 — sexual organs in, 582
 — syphilis as cause, 581
 MONHYBRIDISM, 128
 MONSTROSITIES produced by toxins, 52
 MONTAIGNE on old age, 14
 MOON, effect of, on obesity, 512
 — — on rhythm, 114
 MORAL qualities, relation to deformities, 90
 MORBUS coxæ senilis, see *Arthritis deformans*, 462
 MORPHIA as a toxin, 50
 MORPHŒA, 239
 MORTALITY of alcoholism, 64
 MOTOR cells, degeneration of, 315
 MOUTH, cancer of, 167
 MOUSE tumour, Jensen's, 203
 MUSCLE, disorders of, 246
 — degenerative hyperplasia of, 247
 — emaciation of, 246
 — hypertrophy of, single, 246
 — — of, general, 247
 — in myasthenia gravis, 254
 — in myositis fibrosa, 252
 — — ossificans, 253
 — in myotonia congenita, 251
 — in progeria, 658
 — overgrowth of, 247, 250
 — — associated with sexual precocity, 524
 — — associated with obesity, 507, 515
 — — local, 247
 — — of uterine, 356
 — senilism of, 247
 — undergrowth of, 246
 — varieties of, 247
 MUSCULAR atrophy, progressive, associated with general paralysis, 331
 — degeneration, varieties of, 247
 — dystrophy, 247
 — — age in, 248
 — — alcohol as cause of, 248
 — — anatomy of, 249
 — — associated with infantilism, 567
 — — — with microcephaly, 324
 — — — with scleroderma, 567
 — — associations with, 249
 — — causes of, 248
 — — course of, 249
 — — heredity of, 248
 — — origin of, 250
 — — pathology of, 249
 — — prognosis of, 249
 — — sex in, 249
 — — syphilis as cause of, 248
 — — treatment of, 249
 — — types of, 248
 MUSTER, Pauline, a microcephalic dwarf, 577
 MUTATION, see *Variation*, 100
 MYASTHENIA gravis, 254
 MYCOSIS fungoides, 203, 410
 MYELOMATA, 451
 — relation with osteomalacia, 451
 — — with osteitis deformans, 451
 MYELOPATHIC albumosuria, see *Kahler's disease*, 452
 MYOSITIS fibrosa, 252
 — ossificans, 252
 MYOTONIA congenita, 96, 247, 250
 MYXŒDEMA (thyroid senilism), 643
 — associated with acromegaly, 667
 — senile changes in, 643
 NAPOLEON I, cause of death of, 164
 NŒVI, 148; see also *Telangiectases*.
 NAMPA image, 618-621
 NEANDERTHAL man, 618
 NEGRILLOS, 552
 NEGRITOS, 552
 NELSON, an ateleiosic dwarf, 587
 NEPHRITIS, acute, 301
 — — comparable with hepatitis, 302
 — — distinct from acute Bright's disease, 301
 NERVE-CELLS, in amaurotic family idiocy, 326
 — in general paralysis, 333
 — in senility, 18
 NERVOUS system, defects of, 510
 — — degeneration of, 314
 — — — a devolution, 83
 — — — a reversion, 83
 — — — associated with leukæmia, 400
 — — — with osteomalacia, 449
 — — — with pernicious anæmia, 400
 — — developmental diseases of, as variations, 333
 — — diseases: see also *Insanity*, 314
 — — — associations of, 319
 — — — biology of, 333
 — — — causes of, 316
 — — — childbirth, effect of, 319
 — — — compared with Bright's disease, 315
 — — — with liver cirrhosis, 315
 — — — course of, 317
 — — — heredity of, 333
 — — — list of, 333
 — — — menopause, effect of, 319
 — — — pregnancy, effect of, 319
 — — — remissions in, 317
 — — — structural characters of, 320
 — — — treatment of, 317
 — — infantilism of, 323
 — — — relation to degenerative hyperplasia of extremities, 239
 — — — regressive development of, 328
 NEURONS, peripheral degeneration of, in general paralysis, 332
 — — — in tabes dorsalis, 332
 NEUROPATHIC infantilism, 571
 NICHOLAS Ferry, a case of general senilism, see *Bébé*, 637

- Nose, character of, in acromegaly, 678
 — — in anthropoid apes, 678
 — — in dwarfs, 574
 — — in microcephaly, 573, 637
 — — in old age, 678
 — — in paleolithic man, 678
 — — in progeria, 657, 662
 — disorders of, 244
 — overgrowth of, 41
 NUTT, "Commodore," an ateleiosic dwarf, 587, 588
 NUTRITION, 10, 39
 — defective, 39
 — excessive, 39
 — growth and development, combined in health, 38
 — — separated in disease, 38
 — relation to obesity, 504
 OBESITY, 501
 — alcohol as cause of, 512
 — as a variation, 505, 511, 514
 — associated with arterial sclerosis, 515
 — — with chlorosis, 515
 — — with defects of nervous system, 510
 — — with diabetes, 504, 515
 — — with feminism, 537
 — — with Friedreich's ataxia, 509
 — — with genius, 509
 — — with general gigantism, 509
 — — with gout, 515
 — — with granular kidney, 515
 — — with hirsuties, 509
 — — with infantilism (general), 509
 — — with loss of immunity, 515
 — — with other anomalies, 508
 — — with overgrowth of blood, 515
 — — — of muscle, 515
 — — with sexual defect, 573
 — — with sexual precocity, 509, 528
 — — with supra-renal tumours, 509
 — associations of, 503
 — classification of, 501
 — causes of, 512
 — causing sterility, 488
 — chlorotic, 514
 — consequences of, 515
 — cutaneous system in, 497
 — degeneration in, 505
 — degenerative, 513
 — feminism in, 502, 537
 — heredity in, 511
 — hypopituitarism as cause of, 670
 — Lambert, Daniel, a case of, 508
 — local, see *Macrosomia*, 219
 — masculinism in, 503
 — muscular strength in, 503, 515
 — nutrition in, 504
 — origin of, 513
 — plethoric, 514
 — precocious, 502, 507
 — pregnancy as cause of, 512
 — relation to nutrition, 504
 OBESITY, removal of pituitary body as cause of, 670
 — retrogressive, 513
 — seasonal changes in, 512
 — skin in, 504
 — starvation diet in, 516
 — sterility in, 502, 629
 — thyroid in, 503
 — treatment of, 515
 — types of, 514
 — varieties of, 501
 OBLITERATIVE arteritis, 349
 OEDEMA, persistent hereditary, see *Milroy's disease*, 226, 242
 O'BRYNE, a giant, 488
 OLD age, 14, 31, 84, 195, 543
 — — a simplification, 17
 — — blood in, 411
 — — cancer in, 187, 190, 195
 — — diseases of, 44
 — — embryonic characters in, 19
 — — excesses in, 35
 — — hair in, 475
 — — Hampole on, 14
 — — inco-ordination of, 17
 — — Montaigne on, 14
 — — periosteum in, 459
 — — phagocytosis in, 20
 — — premature, secondary to ateleiosis, 662
 — — — death from, at 8 months old, 660
 — — proliferation of cells in, 18
 — — relation to osteitis deformans, 459
 — — — to osteomalacia, 459
 — — reversion in, 17, 673
 — — simian characters of, 673
 — — structural changes in, 17
 — — symptoms of, 14; see also *Centenarianism*.
 ONTOGENETIC degeneration, 86
 — development, 12
 — dwarfism, 485
 ORGANISM, primitive, prototype of the organ, 26
 ORGANS, adaptation to environment of, 111
 — characters of, 43
 — classification of diseases of, 217
 — comparable with an independent organism, 28
 — defects of development of, 43, 57
 — degeneration of, 80, 82, 104, 133
 — — relations with degeneration of cells, 134
 — definition of, 215
 — derived phylogenetically from organisms, 26
 — disorders of growth of, 56
 — — — a quantitative change, 56
 — hyperplasia of, 132, 216
 — — degenerative, 217
 — hypoplasia, degenerative, 217
 — infantilism of, 216, 336, 357, 378, 567
 — overgrowth of, 39, 216

- ORGANS, senilism of, 43, 88, 217
 — — characters of, 43
 — — undergrowth of, 41, 216
 OSSIFICATION delayed in acromegaly, 673
 — — in ateleiosis, 602, 605, 608
 — — in infantilism, 562
 — — premature in progeria, 653, 654, 662
 — — in senilism, 639
 OSTEITIS deformans, 419, 440
 — — anatomy of, 444, 446
 — — arsenic in, 461
 — — as a variation, 465
 — — associations with, 448
 — — associated with Hodgkin's disease, 401, 447, 448
 — — — with pernicious anæmia, 447
 — — bone-marrow in, 447
 — — cancer in, 451
 — — course of, 468
 — — hereditary in, 455
 — — non-calcifying, plastic, 435
 — — prognosis of, 461
 — — relation to myelomata, 451
 — — — to old age, 458
 — — — to osteogenesis imperfecta, 432
 — — — to osteomalacia, 441
 — — — to tumours, 451
 — — secondary to osteogenesis imperfecta, 436
 — — sex in, 457
 — — structural changes in, 456
 — — treatment of, 461
 — — tumours in, 451
 OSTEITIS, fibrous, 436
 OSTEO-ARTHRITIS, see *Arthritis deformans*, 464
 OSTEOGENESIS imperfecta, 430, 439, 440
 — — age in, 430, 439
 — — anatomy of, 430, 431, 432, 437
 — — associated with club foot, 432
 — — — with general infantilism, 438
 — — — with hare-lip, 432
 — — — with spina bifida, 432
 — — bone in, 430
 — — classification of, 419
 — — consecutive to osteomalacia, 432, 442
 — — degeneration of, 432
 — — dislocation of radius, pre-natal, in, 435
 — — heredity in, 430
 — — osteotomy in, 434
 — — pathology of, 431, 437
 — — periosteum in, 431
 — — physiognomy of, 432
 — — prognosis of, 46
 — — relations with cancer, 436
 — — — with myelomata, 435
 — — — with non-calcifying plastic osteitis, 435
 — — — with osteitis deformans, 432, 435, 436
 — — — with osteomalacia, 436
 — — — with senile osteoporosis, 436
 OSTEOGENESIS imperfecta, tumours in, 433
 — — tarda, 439
 OSTEOMALACIA, 419, 440
 — — anatomy of, 437, 444
 — — as a variation, 465
 — — associations of, 449
 — — associated with Bright's disease, 449
 — — — with Hodgkin's disease, 447
 — — — with leukaemia, 448, 449
 — — — with nervous degeneration, 449
 — — — with osteogenesis imperfecta, 433
 — — — with pernicious anæmia, 447, 448, 449
 — — at puberty, 457
 — — cancer in, 451
 — — causes of, 456
 — — clinical characters of, 451
 — — course of, 460
 — — in degenerative hyperplasia of extremities, 237
 — — geographical distribution of, 460
 — — heredity in, 454
 — — marrow in, 444
 — — at menopause, 457
 — — of humerus, 443
 — — of single bones, 442
 — — of skull, 443
 — — pathology of, 437
 — — pregnancy in, 457, 458
 — — prognosis of, 461
 — — relation with Hodgkin's disease, 447
 — — — with myelomata, 451
 — — — with old age, 458
 — — — with osteogenesis imperfecta, 432
 — — — with tumours, 451
 — — resemblance to osteitis deformans, 441
 — — secondary to osteogenesis imperfecta, 436
 — — senility in, 458
 — — sex in, 456
 — — spontaneous recovery from, 461
 — — structural changes in, 444
 — — treated by ovariectomy, 180, 458, 461
 — — treatment of, 461
 — — tumours in, 451
 — — urine in, 459
 — — varieties of, 459
 — — zoological distribution of, 460
 OSTEOPATHY, see *Osteogenesis imperfecta*, 430
 OVARIES, absence of, affecting skeletal growth, 457
 — — in senilism, 664
 OVARIOCTOMY in cancer of breast, 179
 — — in osteomalacia, 180, 458, 461
 OVERGROWTH, 487
 — — definition of, 80
 — — of blood constituents, 371
 — — of bone, 148
 — — of brain, 40, 321
 — — of cells, 39, 147
 — — of entire body, 42, 487
 — — of extremities, 219
 — — of kidney, 298

- OVERGROWTH of liver, 284
 — of lymph-glands, 375
 — of organs, 40
 — of pituitary body, 668
 — of pylorus, 337
 — of sex, 509
 — of skeleton, 120
 — of spleen, 375
 — of thymus gland, 375
 — of thyroid gland, 668
 — progressive, 41
 — regressive, 41
 — two kinds of, 41; see also *Gigantism*.
- PALEOLITHIC man, 617; see *Man, prehistoric*.
- PANCREAS, fibrosis of, associated with liver cirrhosis, 280
- PANCREATIC infantilism, 183, 562, 581
- PARALYSIS, general, 328; see *General paralysis*.
 — agitans, 334
- PARASYPHILITIC affections, 62
- PARENCHYMATOUS group, 363
- PAYNE, Antony, a giant, 493
- PELVIS, contracted, in osteomalacia, 438, 459
- PENIS, cancer of, 161
- PERIODIC drinking, 68
 — insanity, 317
- PERIODICITY, 112
- PERIOSTEUM, thickening of, in old age, 459
- PERITHELIOMA of colon, 155
- PERNICIOUS anemia, see *Anæmia, pernicious*, 386, 413
- PHAGOCYTES, 20, 27, 81, 382
 — action of, in blood degeneration, 384
 — — in cirrhosis, 288, 289
 — — in kidney degeneration, 312
 — effect of alcohol on, 63
 — functions of, 23, 81, 289
 — — in giant extremities, 235
 — in general paralysis, 333
 — in old age, 20
 — in pernicious anæmia, 387
 — in tabes dorsalis, 333
 — osteoclasts as, 19
 — varieties of, 21, 81
 — versatility of, 81
- PHYLOGENETIC degeneration, 86
 — development, 12
 — dwarfs, 485
 — precedents of modern incidents, 26
- PHYLOGENY of cells, 25
 — of liver, effect on pathology, 289
 — of man, 25
 — of organs, 25
- PITUITARY body, adenoma of, 669
 — as growth centre, 656
 — — atrophy of, 668
 — — cancer of, 658
 — — cysts of, 668
 — — enlargement of, in a dwarf, 602
 — — — in ateleiosis, 656
- PITUITARY body, fibrosis of, 658
 — — hypertrophy of, 668
 — — importance of, 656
 — — in acromegaly, 668
 — — in ateleiosis, 602, 613, 656
 — — in gigantism, 488
 — — in infantilism, 681
 — — in progeria, 655
 — — microscopical characters of, 639
 — — removal of, 670
- PLACEREAU, a microcephalic dwarf, 577
- PLANT-CELLS of marine worms, 433
- PLANT growth, 38
 — — hybridisation, 125
- PLANTS, correlation in, 94
 — Mendel's experiments on, 125
 — rhythmic movements of, 113
- PLETHORIC obesity, 514
- POLYCYTHÆMIA, arsenic in, 369
 — associated with arterial fibrosis, 370
 — — with cardiac fibrosis, 370
 — — with erythromelalgia, 370
 — hemoglobin in, 369
 — in heart disease, 368
 — in pernicious anæmia, 387
 — of high altitudes, 368
 — X rays in, 369
- POLYMORPHONUCLEAR cells, 81
- POLYPUS, bleeding, of the nose, 199
- POST-NATAL errors of development, relation to pre-natal errors, 74
 — — "rests" as antecedents of cancers, 488
- PRECOCIOUS gigantism, see *Gigantism*, 489
 — obesity, 532; see *Obesity*.
- PRECOCITY, 472
 — male, 660
 — sexual, see *Sexual precocity*, 521
- PREGNANCY, blood during, 32, 71
 — bone during, 32, 70
 — changes in, 32
 — facilitating acute yellow atrophy of liver, 275, 277
 — — arthritis deformans, 464
 — — Bright's disease, 305
 — — cancer, 165
 — — degeneration, 70
 — — general paralysis, 330
 — — leukemia, 389
 — — nervous system disease, 319
 — — obesity, 512
 — — pernicious anæmia, 389
 — general betterment in, 32
 — growing pains in, 32
 — heart during, 305
 — illegitimate, facilitating acute yellow atrophy of liver, 277
 — — — eclampsia, 307
 — — — insanity, 319
 — leucocytosis in, 33
 — liver in, 275
 — marrow in, 32
 — mental state of, 319
 — nutrition improved in, 33

- PREGNANCY, osteomalacia in, 458
 — secondary changes in, 32
 PREHISTORIC man, see *Man, prehistoric*, 551, 616
 PRE-NATAL deformities caused by alcohol, 76
 — — — by enteric fever,
 — — — by lead, 75
 — — — by septicæmia, 74
 — — — by syphilis, 75
 — — — by toxins, 52
 — — — by tubercle, 74
 — — endemic occurrence of, 52
 — — in microcephaly, 324
 — — in mongolism, 582
 — — relations to post-natal deformities, 74
 — dislocations, 433, 435
 PRESENILE degenerations, see *Senilism*, 104
 PRIVATION, effect of, on development, 35
 PROGERIA, 645
 — acromegaly opposed to, 656
 — associated with malformation of thumb, 655
 — arteries in, 652
 — beginning at age of eight or nine, 657
 — — in infancy, 646
 — brain in, 652
 — dentition in, 651
 — doubtful cases of, 659
 — fontanelle in, 651
 — genital organs in, 651, 657
 — hair in, 649, 657
 — heart in, 652
 — infantile, 660
 — — characters in, 651
 — Hopkin Hopkins, a case (?) of, 659
 — intestines in, 652
 — muscles in, 651
 — nose in, 657
 — ossification in, 653, 654
 — pathology of, 655
 — pituitary body in, 655
 — senile characters in, 652
 — stomach in, 652
 — thymus gland in, 652
 — tonsils in, 654
 PROGRESSIVE muscular atrophy, 331
 — — — associated with tabes, 331
 PROSENCHYMATOUS degeneration, 261
 PROTOZOON, the prototype of the cell, 26
 PSYCHOSES, hereditary, 78
 PUBERTY, 13
 — bone development at, 457
 — chlorosis at, 374
 — effect on microcephaly, 638
 — hyperplasia of breast at, 257
 — hypertrophy of breast at, 256
 — obesity at, 511
 — origin of disease at, 44
 — precocious, 182, 522, 530, 635
 — second, 13
 PUERPERA hæmorrhagia, 379
 PUERPERAL insanity, 319
 PYGMIES, habits of, 553
 — simian characters of, 552; see also *Infantilism*.
 PYLORUS, degenerative hyperplasia of, 337
 — — — age in, 339
 — — — anatomy of, 341
 — — — associations of, 340
 — — — causes of, 339
 — — — heredity of, 339
 — — — in adults, 338
 — — — prognosis of, 339
 — — — treatment of, 339
 RACE, effect of, on degeneration, 73
 RACHITIS, see *Rickets*, 420
 RACIAL degeneration, 85
 — dwarfism, 485, 542
 — feminism, 539
 — infantilism, 539
 — masculinism, 541
 — senilism, 629
 RADIUM, 178
 — effect of, on cancers, 175
 — — on reproductive tissue, 177
 RAYNAUD'S disease associated with infantilism, 569
 RECTUM, adenoma of, 163
 — cancer of, 163
 — ring cancer of, 344
 REGENERATION, structural changes in, 81
 — of pregnancy, 32
 REMISSIONS in acromegaly, 667
 — in cancer, 168
 — in general paralysis, 318
 — in insanity, 317
 — in leukæmia, 395
 — in liver cirrhosis, 272
 — in progressive muscular atrophy, 318
 — in spinal sclerosis, 318
 — in tabes dorsalis, 318
 RETINAL gliomata, heredity of, 164
 RETROGRESSION in cell development, 19
 RETROGRESSIVE development synonymous with old age, 19
 "RESTS," cell, 152, 182
 — cartilage, 417
 REVERSION, ateleiosis as a, 617
 — cancer as a, 194
 — of man, 673
 — of organs, 81, 107; see *Variation, regressive*.
 RHEUMATIC fever causing infantilism, 560
 RHINITIS atrophic, 244
 — hypertrophic, 244
 RHYTHMS, variations as, 109
 — caloric, 123
 — collective, 114
 — contemporary, 122
 — depressing, 122
 — disorders of, 123
 — erratic, 121
 — importance of, 112
 — in movements of marine worms, 113

- RHYTHMS in movements of plants, latent,
 115, 120
 — — racial development, 551
 — latent, 115
 — lesser, 121
 — object of, 112
 — recurrent, 113
 — seasonal, 113, 121
 — single, 114
 — universality of, 112
 RICKETS, 419, 420
 — ætiology of, 421
 — age of onset of, 421
 — a minor variation, 420
 — anatomy of, 421, 422
 — anæmia in, 424
 — associated with sexual precocity, 423,
 527
 — bones in, 421
 — causes of, 421
 — correlation of growth in, 477
 — environment in, 421
 — general symptoms in, 424
 — inherent tendency to, 421
 — a local overgrowth, 420
 — muscle in, 424
 — origin of, 421
 — pathology of, 421
 — prognosis of, 421
 — resemblance to achondroplasia, 424
 — splenomegaly and, 424
 — symptoms of, 424
 — varieties of, 421
 ROSE Bradford's kidney, 303
 ROUSSEAU, Franz and Karl, ateleiosie
 dwarfs, 587

 SAKAIS, 552
 SAMANGS, 552
 SARCOMA, age in, 196
 — associated with carcinoma, 157
 — — with precocious puberty, 182
 — of breast, 157
 — of liver, 157
 — of uterus, 183
 — sites of, 410; see also *Cancer*.
 SARCOMATOSIS, 191
 — associated with cirrhosis, 293
 SAVAGES, 552, 677
 — effect of alcohol on, 548
 — feminism among, 539
 — Haeckel's division of, 552
 SCLERODERMA, 239
 — associated with infantilism, 567
 SCLEROSIS, arterial, see *Arterial sclerosis*,
 447
 SCHREYERIN, Anna Barbara, a dwarf, 601
 SCOTT, Sir Walter, account of Joseph
 Boruwłaski, 594
 SELLA threica, enlarged, see *Pituitary body*,
 488, 602, 669, 681
 SENILE cells, degeneration of, 18
 — — peripheral decay of, 18
 SENILE cells, phagocytosis of, 21
 — in cirrhosis of liver, 290
 — structural changes in, 17
 — — — comparison with senilism, 83
 — decay, with childish characters, descrip-
 tion of, 15
 — degeneration, 86
 — monstrosity, 660
 SENILISM, 82, 145
 — as a variation, 104, 146
 — biological aspects of, 146
 — characters of, 145
 — comparison with normal senility, 83
 — definition of, 87
 — effect of age on, 107
 — functional characters of, 83, 145
 — general, 473, 626
 — — — acromegaly as, 673
 — — — adaptation in, 627
 — — — adaptative, 632
 — — — as a major variation, 631, 645, 666
 — — — as a minor variation, 631
 — — — associated with arterial sclerosis,
 303
 — — — with diabetes, 664
 — — — liver cirrhosis, 633
 — — — masculinism, 665
 — — — with microcephaly, 333
 — — — with sexual precocity, 635
 — — — with syphilis, microcephaly and
 infantilism, 635
 — — — ateleiosis in, 662
 — — — caused by alcohol, 633
 — — — by depression, 632
 — — — by enteric fever, 633
 — — — by environment, 111, 633
 — — — by gonit, 633
 — — — by hardship, 632
 — — — by infantilism, 637
 — — — by influenza, 633
 — — — by lead, 633
 — — — by malaria, 632
 — — — by syphilis, 633, 637
 — — — by toxins, 633
 — — — causes of, 627
 — — — characters of, 628
 — — — classification of, 627
 — — — consecutive, 662
 — — — correlation in, 627
 — — — correlative, 634
 — — — Craters, a case of, 635
 — — — definition of, 87
 — — — developmental, 629
 — — — diagnosis of, 631
 — — — evolutionary, 629
 — — — fat type of, 628
 — — — individual, 629
 — — — kinds of, 628
 — — — lean type of, 629
 — — — Louis II of Hungary as case of, 635
 — — — of insanitation, 632
 — — — of mixed origin, 637
 — — — primary or essential, 666

- SENILISM, general, primary, evidences of, 673
- — simian characters of, 674
 - — racial, 629
 - — relations with infantilism, 76
 - — secondary, 645
 - — — absence of ovaries in, 665
 - — — associations of, 664
 - — — varieties of, 645
 - — sex defect in, 664
 - — simultaneous with infantilism, 646
 - — Thomas Hall, a case of, 636
 - — toxic, 633
 - local, 239
 - — of arteries, 348
 - — of blood organ, 381
 - — of breast, 257
 - — of cells, 19, 42, 88, 133, 153
 - — of joint areas, 462
 - — of kidney, 299, 303
 - — of liver, 19, 265
 - — of muscle, 247
 - — of organs, 43, 88, 133
 - — of skeleton, 19, 440
 - — of stomach, 337
 - — of thyroid gland, 643
 - — of uterus, 359
 - of cells, see *Cancers*, 133, 153
 - of organs, 48, 58, 133
 - structural changes in, 78, 82, 145
 - — symptomatic, changes in, 145
 - a simplification, 17
- SENILITY, inco-ordination in, 17
- fibrous changes in, 17
 - growth redundance in, 23
- SEX, correlation of, 479
- effect of civilisation on, 517
 - in cancer, 165
- SEXUAL development, defective, in ateleiosis, 591, 595, 602, 605, 608, 612
- — — in chlorosis, 372
 - — — in general infantilism, 569, 577, 584
 - — — in mongolism, 583
 - — — in obesity, 508
 - — — in progeria, 657
 - — — in senilism, 664
 - infantilism, 582
 - organs in ateleiosis, 608, 612
 - — delayed development of, 534
 - — relation with obesity, 488, 502, 506
 - — — with skeleton, 457
 - overgrowth of adults, 531
 - precocity, 521, 636
 - — as a reversion, 522
 - — associated with cancer, 182
 - — — with chlorosis, 527
 - — — with hirsuties, 529
 - — — with hypernephroma, 528
 - — — with obesity, 496, 509, 528
 - — — with pernicious anæmia, 403
 - — — with perspiration, excessive, 528
 - — — with rickets, 433, 527
- SEXUAL precocity associated with senilism, 635
- — — with tumour formation, 528
 - — causes of, 480
 - — course of, 529
 - — examples of, 403
 - — fatal, 530
 - — female, 523
 - — fertility in, 523
 - — heredity in, 528
 - — male, 660
 - — muscular development in, 525
 - — results of, 529
 - — varieties of, 529
 - — voice in, 403
 - protraction, 520
 - undergrowth, 533
 - — in ateleiosis, 597
 - — in feminism, 539
 - — in masculinism, 540
 - — in obesity, 503, 506
 - — temporary, 434
- SHOCK as a toxin, 46
- SILVER as a cause of cirrhosis, 269
- SIMIAN features in acromegaly, 673
- SKELETON, disorders of, 416, 440
- — classification of, 419
 - — infantilism of, 430
 - — overgrowth of, 420
 - — — in acromegaly, 671
 - — senilism of, 440, 441
 - — — clinical aspects of, 454
 - — — heredity in, 454
 - — relation of sexual organs to, 457
 - — see also *Osteitis deformans*, *Osteomalacia*, and *Arthritis deformans*.
- SKIN in general obesity, 504
- SPERMATORRHEA, a disorder of rhythm, 123
- SPINAL cord, fibrous degeneration of, 400
- — — in leukæmia, 400
 - — — in osteomalacia, 449
 - — — in pernicious anæmia, 400
- SPLANCHNOMEGALY, 671
- SPLEEN, absence of, 378
- changes of, in Bright's disease, 279
 - — in general infantilism, 567
 - — in polycythæmia, 369
 - — in splenic anæmia, 407
 - degeneration of, 391
 - — associated with liver disease, 279
 - — varieties of, 391
 - endothelioma of, 391, 405, 410
 - enlargement of, in pernicious anæmia, 390
 - infantilism of, 378
 - overgrowth of, 377
- SPLENIC anæmia, see *Anæmia, splenic*, 389
- SPLENOMEGALY associated with general infantilism, 537
- in adults, 377
 - in childhood, 377
 - in splenic anæmia, 407

- SPLENOMEGALY** in rickets, 424
 — kinds of, 377
SPORT, albinism a, 103
 — ateleiosis, a, 585
 — in plant life, 94
 — major variation, a, 99
SPY, paleolithic man of, 618
STATUS lymphaticus, 371, 375
STERILITY as a major variation, 97
 — a stigma of degeneration, 91, 92
 — associated with acromegaly, 667
 — — with developmental disorders, 358
 — — with growth disorders, 358
 — — with idiocy, 78
 — — — mental deficiency, 78
 — — — obesity, 488, 502, 629
 — caused by alcohol, 77
 — — by emotion, 77
 — — by lead, 77
 — — by privation, 77
 — — by syphilis, 77
 — — by X rays 177
 — effect of heredity on, 129
 — infantilism of uterus in, 359
STIGMATA of degeneration, 89
 — in plant life, 91
 — significance of, 91
STOMACH, anatomy of, 335
 — atrophic degeneration of, 342
 — — — in pernicious anemia, 399
 — — — progeria, 652
 — cancer of, 190
 — carcinomatosis of, 344
 — defective development of, 335
 — disorders of, 336
 — fibrosis of, see *Stomach, senilism of*, 337, 342
 — funnel shaped, 337
 — hyperplasia of, 337
 — — age in, 339
 — — anatomy of, 341
 — — associations of, 340
 — — caused by alcohol, 339
 — — — by gout, 339
 — — causes of, 339
 — — clinical characters of, 339
 — — degenerative, 337
 — — heredity in, 339
 — — prognosis of, 339
 — — relation to cancer, 343
 — — treatment of, 339
 — hypoplasia of, 342
 — infantilism of, 336, 337
 — — consecutive degeneration in, 337
 — overgrowth of, 336
 — senilism of, 337, 342
 — — relations with cancer, 343
 — — — with pernicious anemia, 399
 — stenosis of, 336
 — undergrowth of, 336
STRATTON, Charles, an ateleiotic dwarf, 591
SUPRA-RENAL capsules, atrophy of, 399
SWANN, Miss, a giantess, 491
SYPHILIS causing acromegaly, 666
 — — arterial degeneration, 350
 — — Bright's disease, 304
 — — cancer, 161
 — — degeneration, 61
 — — general paralysis, 329
 — — infantilism, general, 559, 564
 — — insanity, 346
 — — liver cirrhosis, 266
 — — mongolism, 581
 — — muscular dystrophy, 248
 — — senilism, general, 633
 — — sterility, 77
 — — tabes dorsalis, 329
 — changes produced by, 62
 — effect of, combined with alcohol, 67
 — — — with lead as cause of degeneration, 67
 — — on fetus, 75
 — intra-uterine, 633
 — irritative effect of, 61
SYRINGOMYELIA associated with acromegaly, 667
TABES dorsalis, 328
 — — anatomy of, 332
 — — arterial sclerosis in, 333
 — — a reversion, 332
 — — a senilism, 332
 — — associated with general paralysis, 331
 — — — with muscular atrophy, 331
 — — associations of, 331
 — — causes of, 328
 — — civilisation as cause of, 329
 — — comparison with liver cirrhosis, 333
 — — course of, 331
 — — pathology of, 332
 — — phagocytosis in, 333
 — — syphilis as cause of, 328
TALENT, relation to genius, 100
TELANGIECTASES, multiple, 148
 — — causes of, 150
 — — treatment of, 148
 — — with macropody, 221
TESTES, absence of, 157: see *Cryptorchism*.
THOMSEN'S disease (*Myotonia congenita*), 96, 247, 250
THORIUM as substitute for radium, 178
THYMUS gland, functions of, 375
 — — degeneration of, in progeria, 652
 — — overgrowth of, see *Lymphatism*, 376
THYROID extract causing increase of growth, 551
 — — in cretinism, 624
 — — in myxedema, 613
 — — in obesity, 503
 — — in tobacco infantilism, 561
 — gland, adenomata of, 467
 — — degeneration of, 468, 643
 — — — causing obesity, 503
 — — — in senilism, 629
 — — degenerative hyperplasia of, 468
 — — enlarged, in acromegaly, 667

- THYROID gland, enlarged, in gigantism, 492
 — — — in Graves's disease, 467
 — — — in myxœdema, 643
 — — — inadequacy, 549
 — — — in ateleiosis, 602, 608, 612
 — — — infantilism of, 467, 624
 — — — in progeria, 652
 — — — overgrowth of, 467, 668
 — — — senilism of, 467, 643
 — — — undergrowth of, 467
 TIGHT-LACING causing cirrhosis of liver, 269
 TISSUE, chorionic, 156
 — connective, 81
 — effect of radium on, 177
 — granulation, 156
 — lymphatic, 204
 TOBACCO causing arterial degeneration, 351
 560
 — — infantilism, 560, 561
 TOM Thumb (Charles Stratton), 591
 TOPHAM, Thos., a strong man, 247
 TOXIC infantilism, 559
 — senilism, 633
 TOXIN, alcohol as a, 49, 62
 — lead as a, 50
 — morphia as a, 50
 — syphilis as a, 61
 TOXINS, 60
 — alkaloids as, 48
 — bacterial, 47
 — causing Bright's disease, 304
 — — degeneration, 60
 — — general infantilism, 483
 — — liver, acute yellow atrophy of, 277
 — — monstrosities, 52
 — contributory causes of disease, 58
 — disease, 50
 — drugs as, 48
 — effect of, 61
 — — on cancer, 173
 — — on gamete, 125
 — — on germ-cells, 125
 — emotions, strong, as psychical, 46
 — as excretions, 47
 — as forms of insanitation, 483
 — mineral, 61, 269
 — nature of, 47
 — of extrinsic production,
 — of toadstools, 47
 — psychical, 483
 — remedies as, 48
 — saprophytic, 47
 TRANSFORMING heredity, 71, 129
 TRAUMA causing acromegaly, 666
 "TROPIC nerves," 4, 205
 TUMOURS associated with osteitis de-
 formans, 451
 — — with osteogenesis imperfecta, 433
 435, 436
 — — — osteomalacia, 451
 — innocent, 53, 132, 147
 — — causes of, 54, 150
 — — clinical features of, 54
 TUMOURS, innocent, course of, 54
 — — as excesses of growth, 53
 — — of thigh, 433
 — — prognosis of, 55
 — — relation of, to pre-natal malforma-
 tions, 53
 — — structure of, 151
 — — transformation of, into cancers, 49, 54
 — — treatment of, 151
 — malignant, see *Cancer*, 54, 133
 — — associated with sexual precocity, 528
 — — relation of, to innocent growths, 54
 — ovarian, relations with sexual precocity
 182
 — structural characters of, 79
 — two classes of, 53
 ULCERATION in giant hand, 228
 — in macrosomia, 228, 241
 — in rhinitis, 244
 UNDERGROWTH, 485
 — f cells, 39
 — of organs, 41
 URINE in chlorosis, 373
 — in intestinal infection, 562
 — in Kahler's disease, 453
 — in senile osteomalacia, 459
 UTERUS, cancer of, 176
 — hyperplasia, degenerative, of, 359
 — — — amenorrhœa in, 360
 — — — fibro-myomata in, 360
 — — — menorrhagia in, 359
 — — — diagnosis of, from cancer, 359
 — — — from pregnancy, 360
 — hypertrophy of, 360
 — hypoplasia, degenerative of, 362
 — infantilism of, 357
 — — causes of, 358
 — — sterility in, 358
 — overgrowth of, 354, 356
 — — as a variation, 356
 — — associated with chlorosis, 356
 — — caused by metritis, 356
 — — — by pregnancy, 356
 — — comparable with Graves's disease,
 356
 — — diagnosis of, 354
 — — effect on menstruation, 355
 — — origin of, 356
 — senilism of, 359
 — — symptoms of, 359
 — — varieties of, 359
 — — sub-involution of, see *Uterus, over-
 growth of*, 354, 357
 — undergrowth of, 354
 VARIATION, achondroplasia as a, 428
 — acromegaly as a, 666
 — adaptation and, 110
 — arthritis deformans as a, 465
 — associated with sterility, 97
 — Bright's disease as a, 107
 — centenarianism as a, 546

VARIATION, cirrhosis as a, 291
 — definition of, 99
 — feminism as a, 536
 — in evolution, 99
 — kinds of, 100
 — major or discontinuous, 101
 — — albinism as a, 103, 104
 — — genius as a, 100
 — — masculinism as a, 341
 — — relation to minor, 137
 — minor or continuous, 101, 557
 — — liver cirrhosis as a, 104
 — — relation to major, 137
 — — talent, a, 100
 — of cells, 210
 — of man, 517
 — of organs, 94, 95
 — of plants, 94, 97
 — origin of, 108, 116
 — osteitis deformans as a, 465
 — osteomalacia as a, 465
 — pathological, 103
 — — origin of, 119

VARIATION, progressive, 100, 102, 119
 — regressive, 100, 120, 126, 128, 130
 — rickets as a, 42
 — senilism, general, as a, 634
 — symptomatic infantilism as a, 548
 VAULT of skull, defective development of, 324

VITALITY, see *Nutrition*, 10

WARREN, Lavinia, an ateleiosic dwarf, 591
 WORMS, marine, 113

X RAYS causing sterility, 177
 — effect of, on cancer-cells, 175, 208
 — — on granuloma fungoides, 204
 — — on leucocytes, 208
 — — on polycythæmia, 369
 — — on sex organs, 178

YOUTH, 31

ZIMMERMANN, Balthazar, a dwarf, 595
 ZYGOTES, 136





Ex Libris

JAMES WALKER DAWSON

